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SPECIAL ARTICLE

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 more than 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. There is an inherited genetic susceptibility for CLL, with a sixfold to ninefold increased risk for family members of patients with CLL.

Recommendation

- Routine screening for CLL is not recommended either in the general population or in relatives of patients with CLL [V, E].

DIAGNOSIS AND PATHOLOGY/MOLECULAR BIOLOGY

The diagnosis of CLL is established by the following criteria:[1,2]

- Presence of $\geq 5 \times 10^9$/l monoclonal B lymphocytes in the peripheral blood. The clonality of the circulating B lymphocytes needs to be confirmed by demonstrating light chain restriction using 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%.[1]

CLL cells co-express the B-cell surface antigens CD19 and CD20 together with CD5, CD23, CD43 and CD200. The levels of surface CD20, surface immunoglobulin (Ig) and CD79b are characteristically low compared with those found on normal B cells.[3] Each clone of leukaemia cells is restricted to expression of either kappa or lambda Ig light chains, or has no apparent expression of either of the two.

Other lymphoma entities to be differentiated from CLL are mantle cell lymphoma (MCL), leukaemic marginal zone lymphoma (MZL) (in particular the splenic variant) and lymphoplasmacytic lymphoma. These tumour cells may express B-cell surface antigens and CD5, but in most cases, they do not express CD23, in particular MZL. For cases that express CD23, reverse transcription polymerase chain reaction (RT-PCR) for determination of cyclin D1 overexpression, and FISH for detecting a translocation (11;14), but also CD200 expression, are useful for establishing the diagnosis of MCL. Additionally, SOX11 staining may be used on tumour biopsies. A diagnosis of

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MZL is supported by negative or low CD43 expression and high expression of CD180.[4]

In the World Health Organization (WHO) classification from 2017 as well as in prior versions, small lymphocytic lymphoma (SLL) and CLL are considered a single entity. If B lymphocytes in the peripheral blood are $<5 \times 10^9$/l and lymphadenopathy and/or splenomegaly (detected by either physical examination or imaging studies) is present, SLL instead of CLL is diagnosed. SLL cells show the same immunophenotype as CLL. Although SLLs have a circulating clone, the diagnosis of SLL should be confirmed by histopathologic evaluation of a lymph node (LN) biopsy whenever possible.

In the absence of lymphadenopathy, organomegaly, cytopaenia and clinical symptoms, the presence of $<5 \times 10^9$/l monoclonal B lymphocytes defines 'monoclonal B lymphocytosis' (MBL),[2] which can be detected in up to 5% of subjects with normal blood count with frequency increasing with age.[5] Progression to CLL occurs in at least 1%-2% of MBL cases per year.[5] It may be important to point out to patients and healthy individuals that MBL is not yet a leukaemia or lymphoma.

Recommendations

- Diagnosis is usually possible by immunophenotyping of peripheral blood only [III, A].
- LN biopsy and/or bone marrow biopsy may be helpful if immunophenotyping is not conclusive for the diagnosis of CLL [IV, A].

STAGING AND RISK ASSESSMENT

Early, asymptomatic stage

Early, asymptomatic stage disease, as determined by either the Rai or the Binet staging system, (Table 1) does not need further risk assessment (see section below 'Management of early disease').

After the first year, when all patients should be seen at 3-monthly intervals, patients can be followed every 3-12 months depending on burden and dynamics of the disease by the following recommended examinations (Table 2):

- History and physical examinations including a careful palpation of all LN areas, spleen and liver;
- Complete blood cell count and differential count.

Advanced or symptomatic stage

The following examinations are recommended before treatment [III, B] (Table 2):[2]

- History and physical examination including a careful palpation of all LN areas, spleen and liver;
- Complete blood cell count and differential count;
- Serum chemistry including lactate dehydrogenase (LDH), bilirubin, serum Igs, direct antiglobulin test (DAT) and haptoglobin. Other parameters in order to exclude other reasons for existing anaemia may be carried out. In addition, kidney and liver function should be tested before starting systemic therapy;
- The history and status of relevant infections [i.e. hepatitis B (HBV) and C (HCV), cytomegalovirus (CMV), human immunodeficiency virus (HIV)] should be evaluated to prevent virus reactivation;

Table 1. Staging systems for CLL

Stage		Definition
Binet system		
Binet A		Hb $\geq$100 g/l (6.21 mmol/l), platelets $\geq 100 \times 10^9$/l $<$3 involved lymphoid sites[a]
Binet B		Hb $\geq$100 g/l (6.21 mmol/l), platelets $\geq 100 \times 10^9$/l $\geq$3 involved lymphoid sites[a]
Binet C		Hb $<$100 g/l (6.21 mmol/l), platelets $<100 \times 10^9$/l
Rai system		
Low-risk	Rai 0	Lymphocytosis $>5 \times 10^9$/l
Intermediate-risk	Rai I Rai II	Lymphocytosis and lymphadenopathy Lymphocytosis and hepatomegaly and/or splenomegaly with/without lymphadenopathy
High-risk	Rai III	Lymphocytosis and Hb $<$110 g/l (6.83 mmol/l) with/without lymphadenopathy/organomegaly
	Rai IV	Lymphocytosis and platelets $<100 \times 10^9$/l with/without lymphadenopathy/organomegaly

Originally described overall survival times were deleted, because they have changed during the past 30 years[81] but do not reflect the impact of novel treatments.
CLL, chronic lymphocytic leukaemia; Hb, haemoglobin.
[a] Binet's system takes into account five potential sites of involvement: cervical, axillary, inguinal lymphadenopathy (either uni- or bilateral), spleen and liver. Involvement is judged only by physical exam and does not take into consideration the results of imaging studies for staging purposes.
Adapted from Binet et al.[13] with permission and Rai et al.[14]

Table 2. Diagnostic and staging work-up

	Initial staging at diagnosis	Pre-treatment evaluation	Staging at the end of therapy	Follow-up
History, physical examination and performance status	+	+	+	+
Complete blood count and differential	+	+	+	+
Serum chemistry including serum immunoglobulin and direct antiglobulin test	–	+	+	+
Cytogenetics (FISH) and molecular genetics for *TP53* mutation or *del(17p)*	(+)[a]	+	–	–
IGHV mutational status	(+)[a]	+	–	–
Marrow aspirate and biopsy	–	+[b]	+[c]	–
HBV, HCV, CMV and HIV serology	–	+	–	
Radiological imaging (CT scan)	–	+[d]	+[d]	

CMV, cytomegalovirus; CR, complete remission; CT, computed tomography; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IGHV, immunoglobulin heavy chain variable.
[a] Only if patient requests the evaluation of his prognostic score.
[b] Only if clinically indicated.
[c] Only for confirmation of CR within clinical studies.
[d] Only within clinical studies, in patients with clinical symptoms and before any venetoclax treatment.

- FISH for detection of deletion of the chromosome 17 [del(17p)] affecting the tumour protein p53 expression and, in the absence of del(17p), *TP53* sequencing for detection of *TP53* gene mutation (at least exons 4-10, exons 2-11 recommended) [III, A].[6] Array-based techniques might be used alternatively to FISH in the future,[7] but most data for the prognostic and predictive value of *TP53* deletion are based on FISH. As genetic lesions may evolve throughout the disease, the analysis should be carried out as close as possible (e.g. $<$6 months) to initiation of therapy (Table 3);
- Molecular analysis for detecting Ig heavy chain variable (IGHV) gene mutation status (Table 3);[8]
- Chest imaging: see section 'Imaging'.

The following additional examinations before treatment are desirable [III, B]:[9]

- Although a bone marrow examination is not required for diagnosis, it is recommended for the diagnostic evaluation of unclear cytopaenia or in the presence of a non-conclusive phenotype. A marrow biopsy may be considered as a baseline parameter to assess treatment response;
- An extended FISH analysis (or array-based analysis) before therapy may allow the detection of additional cytogenetic abnormalities [e.g. del(11q) or trisomy 12];
- Hepatitis E testing is optional but should particularly be considered if the patient is positive for HBV;[10]
- Serum β2-microglobulin (B2M) is an important prognostic marker, which is part of the CLL-International Prognostic Index (IPI).[11]

Imaging. Radiographic imaging [computed tomography (CT) scan, magnetic resonance imaging (MRI)] is not generally recommended in asymptomatic patients. Radiographic imaging with CT scan is recommended in symptomatic patients, for example in pulmonary symptomatic patients, in order to exclude pulmonary infiltration or pleural effusion by CLL. MRI, chest radiography or abdominal ultrasound (US) may be considered as alternatives if there are contraindications against CT scan or a scan is not available.

In general, CT scans of neck, chest, abdomen and pelvis or MRI may be helpful to assess the tumour load and risk of tumour lysis syndrome (TLS), particularly before treatment with the BCL2 inhibitor venetoclax. In addition, CT scans may be useful for baseline and final assessment in clinical trials,[12] as well as for response evaluation for patients in clinical practice [III, C]. In elderly patients, US and radiographic chest imaging might be considered instead for CT scans.

Prognostication

Two clinical staging systems are used in CLL (Table 1).[13,14] Both Binet and Rai staging systems separate three groups of patients with different prognosis (Table 1).[13,14] As a consequence of more effective therapy, the overall survival (OS) of patients with advanced stage has improved[15] and the relevance of the staging systems for prognostication has decreased.

Table 3. Personalised medicine synopsis

Biomarker	Method	Use	LoE, GoR
TP53 mutation or *del(17p)*	FISH and Sanger or NGS	Strongest prognostic and predictive relevance together with del(17p)	III, A
IGHV	Sanger or NGS	Strong prognostic evidence; predictive evidence for CIT	III, A
Complex karyotype	Chromosome banding	Possible prognostic and predictive relevance but not yet established prospectively	IV, C

CIT, chemoimmunotherapy; GoR, grade of recommendation; IGHV, immunoglobulin heavy chain variable; LoE, level of evidence; NGS, next-generation sequencing.

Additional markers are available to predict the prognosis of patients with CLL. Patients with a detectable del(17p) or a mutation of *TP53* have the poorest prognosis at least in the era of chemoimmunotherapy (CIT), with a median OS of 2-5 years.[16,17] The prognosis of those patients has significantly improved with the introduction of B-cell receptor inhibitors (BCRis)[18] and the BCL2 inhibitor venetoclax. Nevertheless, subgroup analyses of trials show that *TP53* appears to maintain its poor prognostic and predictive impact even with some inhibitor therapies. The formerly poor prognosis of patients with a del(11q) ($\sim$20%) has been strongly improved by CIT with fludarabine, cyclophosphamide and rituximab (FCR) and by novel targeted agents such as BCRis and venetoclax.[19-21] Other gene mutations such as *NOTCH1*, *SF3B1* or *BIRC3*, *RPS15*[22,23] as well as complex karyotype (CKT) (defined by $\geq$3 or $\geq$5 abnormalities in chromosomal banding analysis) predict an unfavourable prognosis in the absence of *TP53* deletion/mutation and should be studied in clinical trials [III, C].[24-27] Because leukaemic clones may evolve, FISH for del(17p) and *TP53* mutation analyses should be repeated before any line of therapy [III, A].[28]

Around 60% of patients with CLL in need of treatment have an unmutated IGHV status.[29,30] CLL cells with unmutated IGVH status have a higher genetic instability with a higher risk of presenting unfavourable genetic mutations. OS and time to treatment intervention are significantly shorter in this patient group [III, A].

To create a comprehensive tool for predicting the outcomes of patients with CLL, different prognostic scores have been proposed.[11,31,32] The CLL-IPI includes stage, age, *TP53* status, IGHV status and serum B2M and distinguishes four different prognostic subgroups predicting OS.[11] The CLL-IPI has been extensively validated.[33,34] This prognostic model was designed to identify three groups of patients: (i) patients that should not be treated (low-risk), because they show a very good prognosis without therapy;

(ii) patients that usually show a reasonably good outcome with CIT (intermediate- and intermediate/high-risk), in particular when novel agents are not available for first-line therapy; and (iii) patients that should receive targeted agents as front-line therapy, because chemotherapy (ChT) is ineffective (very high-risk).[33] However, with the increasing use of targeted agents in front-line independent from patient risk factor profile, the role of CLL-IPI will have to be further determined.[33]

Goals of therapy

Since in most cases CLL remains an incurable disease, the goals of therapy are to improve quality of life and to prolong survival. In daily life, important treatment end points in clinical trials, such as response rate, minimal residual disease (MRD) status or progression-free-survival (PFS), may be more relevant for young and/or fit patients than in older patients and/or patients with relevant comorbidity. Ultimately, in most patients, survival depends on the effect and choice of treatment sequences given along the course of the disease.

Recommendations

- Binet and Rai staging systems with clinical symptoms are relevant for treatment indication [III, A].
- del(17p), *TP53* mutations and IGHV status are relevant for choice of therapy and should be assessed before treatment [III, A].
- Routine evaluation of del(17p), *TP53* mutation and IGHV status in early and asymptomatic stage is not recommended [V, D].
- Routine imaging during a watch-and-wait period is not recommended unless there are clinical symptoms [V, E].

MANAGEMENT OF EARLY 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 chemotherapeutic agents does not translate into a survival advantage in patients with early-stage CLL.[35,36] Results of clinical trials evaluating early treatment with novel agents are still pending. 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 after the first year, when 3-monthly intervals should be applied for all patients.

Due to the lack of clinical trials, no evidence-based treatment recommendation can be given for localised, early-stage SLL, but there is consensus that the management of SLL is similar to CLL. Locoregional radiotherapy may only be considered for symptomatic lymphadenopathy in selected patients with localised SLL.

Recommendation

- The standard treatment of patients with early asymptomatic disease is a watch-and-wait strategy [I, A].

MANAGEMENT OF ADVANCED DISEASE

Binet stage A and B with active disease or Binet stage C; Rai 0-II with active disease or Rai III-IV

In general, whenever possible, patients should be treated within a clinical trial for all lines of therapy.

Treatment indication. Whereas patients with intermediate- (stage I and II) and high-risk (stage III and IV) disease (according to the modified Rai classification or at Binet stage B or C) usually benefit from the initiation of treatment, some of these patients (in particular Rai intermediate-risk or Binet stage B) can be monitored without therapy until they have evidence for progressive or symptomatic disease (summarised as 'active disease').[2] 'Active disease' should be clearly documented to initiate therapy. At least one of the following criteria should be met:[2]

- Evidence of progressive marrow failure as manifested by the development of, or worsening of, anaemia and/or thrombocytopaenia. Cut-off levels of haemoglobin (Hb) <100 g/l (<6.21 mmol/l) or platelet counts $<100 \times 10^9$/l are generally regarded as indications for treatment. However, it should be pointed out that in some patients, platelet counts $<100 \times 10^9$/l may remain stable over a long period of time; this situation does not automatically require therapeutic intervention;
- Massive (i.e. $\geq$6 cm below the left costal margin) or progressive or symptomatic splenomegaly;
- Massive (i.e. $\geq$10 cm in longest diameter) or progressive or symptomatic lymphadenopathy;
- Progressive lymphocytosis with an increase of $\geq$50% over a 2-month period, or lymphocyte doubling time (LDT) of $<$6 months. LDT can be obtained by linear regression extrapolation of absolute lymphocyte counts (ALCs) obtained at intervals of 2 weeks over an observation period of 2-3 months; patients with initial blood lymphocyte counts of $<30 \times 10^9$/l may require a longer observation period to determine the LDT. Factors contributing to lymphocytosis other than CLL (e.g. infections, steroid administration) should be excluded particularly when LDT is the only criterion to start therapy;
- Autoimmune complications including anaemia or thrombocytopaenia poorly responsive to corticosteroids;
- Symptomatic or functional extranodal involvement (e.g. skin, kidney, lung, spine);
- Disease-related symptoms as defined by any of the following:
  - Unintentional weight loss $\geq$10% within the previous 6 months;
  - Significant fatigue [i.e. European Cooperative Oncology Group performance status (ECOG PS) 2 or worse; cannot work or unable to perform usual activities];
  - Fevers $\geq$38.0°C for $\geq$2 weeks without evidence of infection;
  - Night sweats for $\geq$1 months without evidence of infection.

Factors contributing to these symptoms other than CLL (e.g. secondary neoplasia, infections, sleep disorders, anxiety, menopause) should be excluded, in particular when any of these symptoms is the only criterion to start therapy.

Front-line treatment. For front-line therapy, different treatment strategies are available (Figure 1); continuous treatment with Bruton tyrosine kinase inhibitors (BTKis) such as ibrutinib until progression or time-limited therapy with ChT backbone and CD20 antibodies. In addition, the United States Food and Drug Administration (FDA) and European Medicines Agency (EMA) have recently approved the combination of venetoclax plus obinutuzumab as first-line therapy for CLL.[21] Hence, this time-limited, CIT-free regimen is an alternative third option. The treatment decision should include an assessment of IGHV and *TP53* status, as well as patient-related factors such as comedication, comorbidities, preferences, drug availability and potential of treatment adherence.

Therapy until progression with ibrutinib alone or in combination with CD20 antibodies has yielded a longer PFS when compared with fixed duration CIT [FCR, bendamustine plus rituximab (BR), chlorambucil plus obinutuzumab] in phase III randomised trials [I, A].[37-39] However, the optimal duration of treatment with ibrutinib has not been defined. Data of one phase III trial which compared ibrutinib plus rituximab versus FCR in young and fit patients suggest that an OS benefit for ibrutinib-treated patients might exist.[37] Two published trials, which allowed a crossover to ibrutinib in patients progressing after CIT, have shown no difference in OS so far.[38,39] The Alliance trial compared BR versus ibrutinib alone versus ibrutinib plus rituximab in patients aged ≥65 years and showed no difference between both ibrutinib-containing arms, but a significant difference in PFS for both ibrutinib-containing arms versus BR (74% versus 87% and 88% at 2 years, respectively).[38] Within the ILLUMINATE trial, patients >65 years of age or with significant comorbidity were randomised between chlorambucil plus obinutuzumab (for 6 months) and ibrutinib plus obinutuzumab. A significantly different PFS was estimated at 30 months at 79% [95% confidence interval (CI) 70-85] in the ibrutinib plus obinutuzumab group versus 31% (95% CI 23-40) in the chlorambucil plus obinutuzumab group, while a third arm with ibrutinib monotherapy was missing.[39]

The ELEVATE study investigated the BTKi acalabrutinib alone or in combination with obinutuzumab in comparison with CIT with chlorambucil plus obinutuzumab in elderly patients with CLL.[40] The study showed a clear benefit for both acalabrutinib-containing arms with respect to PFS [hazard ratio (HR) 0.10 (95% CI 0.06-0.17) for acalabrutinib plus obinutuzumab; HR 0.20 (95% CI 0.13-0.30) for acalabrutinib alone]. Unfortunately, the study is not powered for showing a benefit of adding obinutuzumab to acalabrutinib. Therefore, the potential benefit of obinutuzumab addition to BTKi remains unclear, while it was already demonstrated that there is no benefit by adding rituximab to ibrutinib with respect to disease control in elderly[38] and more fit patients with unfavourable genetic profiles.[41] Subgroup analyses of three out of four trials failed to demonstrate a significant benefit for indefinite ibrutinib or acalabrutinib therapy when compared with fixed-duration CIT in patients with mutated IGHV disease.[38,40,42]

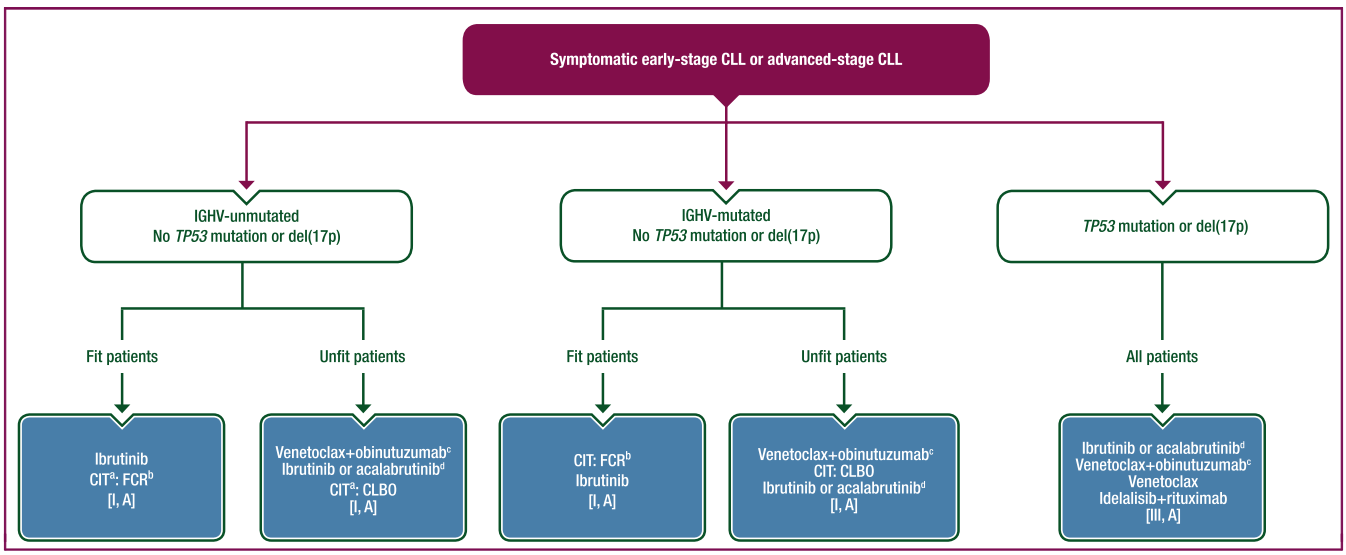

Figure 1. Front-line therapy.
The order of the recommended treatments for each subgroup is based on expert opinion considering time-limited as more valuable therapy, if there is equal evidence for two different treatment options.
BR, bendamustine plus rituximab; CIT, chemoimmunotherapy; CLBO, chlorambucil plus obinutuzumab; CLL, chronic lymphocytic leukaemia; FCR, fludarabine, cyclophosphamide and rituximab; IGHV, immunoglobulin heavy chain variable.
[a] CIT as alternative treatment, only if reasons against treatment with targeted therapies or non-availability.
[b] BR might be considered alternatively in patients above the age of 65 years.
[c] If available.
[d] If approved and available.

Venetoclax plus obinutuzumab, as time-limited therapy for 12 months, was compared with chlorambucil plus obinutuzumab (for 12 months) in comorbid patients.[21] The data of the CLL14 trial showed after 28 months (median observation time) a PFS of 88% at 24 months for the venetoclax combination versus 64% for the CIT group.[21] Subgroup analyses for IGHV-mutated disease also demonstrated a significant benefit for venetoclax plus obinutuzumab compared with chlorambucil plus obinutuzumab as well as for unmutated IGHV disease [mutated IGHV HR 0.33 (CI 0.16-0.70); unmutated IGHV disease HR 0.23 (CI 0.15-0.35)].[43] So far, no difference in OS has been observed. Venetoclax plus obinutuzumab combination, if available, would be the preferred therapy in comparison with CIT for patients with comorbid conditions [I, A].

Because data for fit patients are not yet available for venetoclax plus obinutuzumab, no clear recommendation can be given for this group, but it is expected that this combination will also show superiority in this setting.

For the choice between venetoclax plus obinutuzumab versus ibrutinib or other BTKis, time-limited therapy would be preferred, but side-effect profile (renal impairment and risk of TLS versus atrial fibrillation and bleeding risk), application mode [intravenous (i.v.)] application with combination therapy due to the antibody infusion versus oral medication only], intensity of controls (5-week ramp-up period with the combination) and shorter follow-up have to be taken into consideration [V, B].

CIT may still be considered an appropriate first-line therapy for fit patients with CLL and mutated IGHV status [II, B].[44,45] In counselling with patients, the long-term risk of CIT to induce secondary neoplasia, leukaemias/myelodysplastic syndromes (MDS) and infections should be taken into consideration. Similarly, a history of concurrent atrial fibrillation, ventricular arrhythmias or other cardiovascular disorders, concomitant antiplatelet or anticoagulation therapy, comedication or compliance problems, should be considered and discussed with the patient before starting BTKi therapy.[46,47] For the necessary ramp-up of venetoclax, accessibility to the medical centre for patients considered for venetoclax-obinutuzumab should be discussed, as well as the lack of long-term follow-up data.

For patients to be treated with CIT, young and fit patients with CLL should receive FCR therapy [I, A].[19] BR should be considered for fit patients aged >65 years due to increased rates of infections and secondary myeloid neoplasia with FCR (Figure 1) [I, A].[48-50] In patients with significant comorbidity, chlorambucil plus obinutuzumab can be considered, if treatment with targeted agents is not an option, which might also be used in fit elderly patients though no data are available in this group.[49,50]

Patients with *TP53* mutation or del(17p) should receive front-line therapy with BTKis [III, A]; CIT is not an option due to the poor prognosis with this therapy independent from IGHV status.[19] Ibrutinib therapy may raise concerns due to the history of concurrent arrhythmias, significant cardiovascular comorbidity, concomitant antiplatelet or anticoagulant therapy or concomitant therapy with strong CYP3A4 inhibitors, including antiarrhythmics or antihypertensives (which cannot be changed to alternative drugs). If available, other BTKis might have a different side-effect profile, at least with respect to the incidence of arrhythmias.[51,52] Alternatively, the BCL2 inhibitor venetoclax as continuous monotherapy or also time-limited therapy with venetoclax plus obinutuzumab (if approved and available) would be the preferred option [III, A]. A subgroup analysis of the CLL14 trial has also demonstrated less efficacy of venetoclax plus obinutuzumab in *TP53* mutation or del(17p), though the difference was much less than in the CIT arm.[21] The phosphoinositide 3 kinase (PI3K) inhibitor idelalisib plus rituximab may be used in patients who are not eligible for any other therapies [III, A].

Treatment of relapse and refractory disease. As in first-line therapy, treatment at relapse should only be started in symptomatic patients and not simply at the time of reappearance of the disease (Figure 2).[2] Many patients with relapsed but asymptomatic CLL can be followed without therapy for a long period of time. Even stopping continuous medication BCRi (ibrutinib or other BTKis or idelalisib) or venetoclax (for example because of side-effects) does not necessarily require immediate alternative treatment, particularly if CLL is in remission. In the case of rapid progression on targeted agents, immediate change of therapy is recommended.

In case of symptomatic relapse within 3 years after fixed-duration therapy or non-response to therapy,[53] the therapeutic regimen should be changed, regardless of the type of first-line therapy (CIT or novel therapies).

One of the two following treatment options should be chosen [I, A]:

- Venetoclax plus rituximab for 24 months;[54]
- Ibrutinib or acalabrutinib or other BTKis (if available) as continuous therapy.[55-57]

Alternative options include:

- The PI3K inhibitor idelalisib in combination with rituximab [II, B];[58]
- CIT unless a *TP53* mutation or del(17p) is found and no other treatment options with inhibitors or cellular therapy are available; a response to prior BR should have lasted at least 3 years to justify re-administration [II, B]. Repeated administration of FCR is not recommended due to increased toxicity rates and risk of secondary myeloid neoplasm [V, B].

For the choice between these treatment modalities, the following aspects should be discussed with the patient:

- Treatment duration (no termination versus fixed duration);
- Administration [oral (p.o.) versus i.v.];
- Compliance (i.v. versus p.o.);

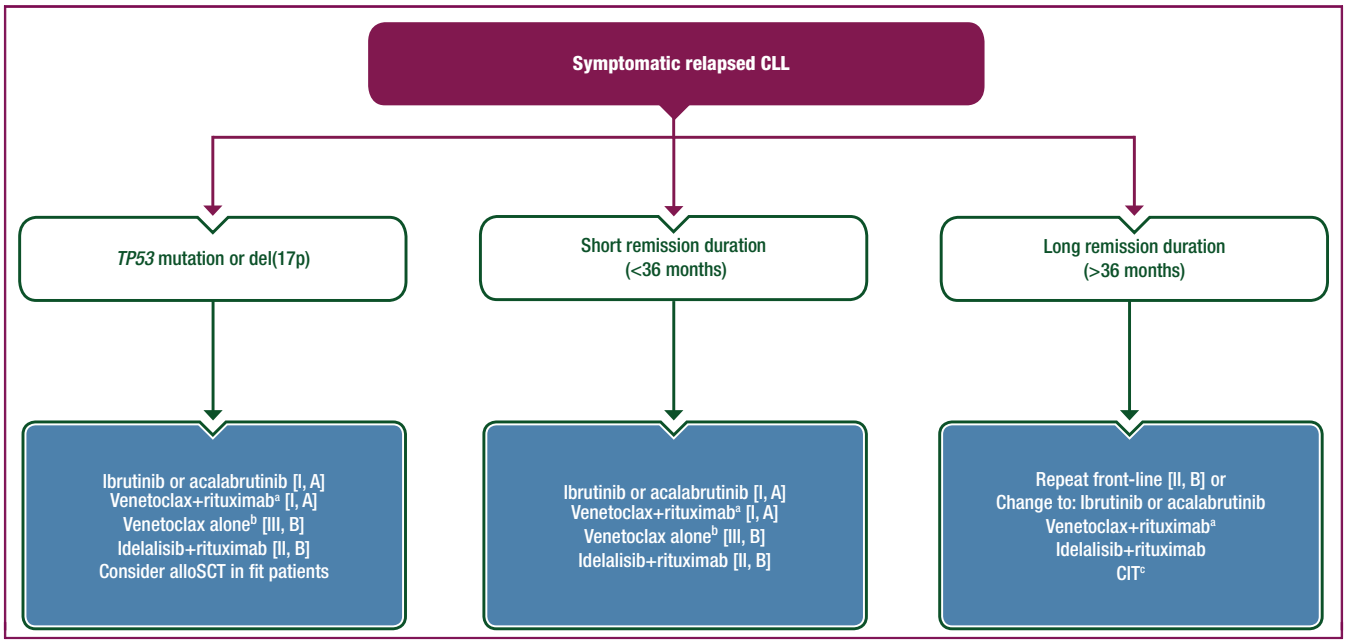

Figure 2. Relapse therapy.
alloSCT, allogeneic stem cell transplantation; BCRi, B-cell receptor inhibitor; CIT, chemoimmunotherapy; CLL, chronic lymphocytic leukaemia; FCR, fludarabine, cyclophosphamide and rituximab; R, rituximab.
[a] After prior ibrutinib, preferred therapy.
[b] After prior CIT and BCRi.
[c] Repetition of FCR not recommended.

- Evidence (currently, more data exist on ibrutinib first-line followed by venetoclax second-line than on the reverse sequence);
- Risk of complications (in particular in the presence of specific comorbidities: bleeding and cardiac comorbidities with ibrutinib or other BTKis versus impaired renal function and neutropaenia with venetoclax);
- Response to and side-effects of prior therapies;
- Number and complexity of clinical controls (2-4 weeks for ibrutinib versus dose ramp-up with three controls every week for 5 weeks to prevent TLS and potential hospitalisation in case of high TLS risk with venetoclax).

In case of progression on BCRi therapy after prior CIT, venetoclax-based therapy is the preferred treatment,[59,60] as change to a different CIT or BCRi does not induce long-lasting remissions [III, B].[61]

In case of long-lasting remissions (>3 years) to prior time-limited therapy, patients may be re-exposed to the same treatment regimen, though data are limited with no long-term observation [II, B].[62]

Role of haematopoietic stem cell transplantation and cellular therapies. Autologous stem cell transplantation (autoSCT) is not useful in CLL [I, D].[63] Allogeneic stem cell transplantation (alloSCT) should be considered[64] in:

- Patients refractory to CIT with *TP53* mutation or del(17p), but fully responsive to novel inhibitor therapy. AlloSCT should be discussed with the patient as an option for curative treatment if risk of transplantation is low;[65]
- Patients refractory to CIT and to novel inhibitor therapy, even for patients with a higher risk of non-relapse mortality [haematopoietic cell transplant comorbidity index (HCT-CI) score of ≥3] [III, B];[65]
- Patients with Richter's transformation in remission after therapy and clonally related to CLL.

Treatment with chimeric antigen receptor T (CAR-T) cells or bi-specific T-cell engager (BiTE) antibodies within clinical trials could be an alternative to alloSCT for all three groups [V, B]. While there is less experience with CAR-T cell therapy in CLL, it is very different from alloSCT in at least two aspects:

- Lower non-relapse mortality and different, mostly acute, toxicity (cytokine release syndrome; CAR-T-cell-related encephalopathy syndrome) which renders this approach available to patients with some comorbidities;
- Uncertain long-term curative potential.

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'[66] and from the 'International Workshop on CLL guidelines'.[9] Most patients with autoimmune cytopaenia, specifically those with warm auto-antibodies, respond to high-dose corticosteroids [III, B]. For patients not responding to corticosteroids, rituximab alone or in combination with cyclophosphamide and dexamethasone might be a reasonable treatment option,[67] as well as BR[68] [III, B]. Recently, BCRis have also shown

promising efficacy [III, B].[69] In patients with resistant autoimmune cytopaenia, treatment of the underlying CLL is recommended before considering splenectomy.

Infectious complications are common in patients with CLL. Therefore, the use of immunosuppressive agents, for example corticosteroids, should be restricted. The use of prophylactic systemic Ig replacement therapy does not have an impact on OS,[70] and is only recommended in patients with severe hypogammaglobulinaemia and repeated or severe infections [I, A]. Antibiotic and antiviral prophylaxis should mostly be used in patients with recurrent infections and/or very high risk of developing infections (for example, pneumocystis prophylaxis with co-trimoxazole during treatment with CIT based on purine analogues or idelalisib) [IV, B]. The risk of fungal infections seems to be increased in patients receiving ibrutinib, particularly when corticosteroids are applied concomitantly.[71] Because of potential drug interactions and the low incidence of fungal infections, routine antifungal prophylaxis is currently not recommended.

Though mortality in patients with bloodstream infections before the start of therapy is elevated in patients with CLL, there are currently no data available supporting the prophylactic use of any antibiotics in early-stage CLL.[72] However, pneumococcal vaccination as well as seasonal flu 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 and MRD assessment should be carried out to define complete remission and MRD status within clinical trials [III, B] as well as CT scans [IV, C].[2] For evaluation of response outside clinical trials, bone marrow biopsy and CT scan may be helpful but are not mandatory. For evaluation of efficacy of novel treatments with continuous administration within clinical trials, more than one CT scan might be necessary.

Detection of MRD by multicolour flow cytometry or RT-PCR has a strong prognostic impact following CIT[73,74] as well as venetoclax plus CD20-antibody combinations.[75] Patients with undetectable MRD after therapy show a longer response duration and survival. Additional clinical consequences of MRD positivity after therapy with respect to treatment escalation remain unclear, except for patients who underwent alloSCT, where a positive MRD signal may trigger the reduction of immunosuppressive therapies, the administration of donor lymphocyte infusions or the start of antileukaemic maintenance therapy. Therefore, MRD assessment is not generally recommended for monitoring after therapy outside clinical studies. This may change soon, as increasing efforts are made to determine whether therapy with targeted agents could be discontinued on the basis of MRD status.[75-77]

Recommendations

- Decision for type of front-line treatment is based on *TP53* mutation or del(17p), IGHV mutational status, age, comorbidities and comedication [II, A].
- CLL with unmutated IGHV status and without *TP53* mutation or del(17p) (if there was similar efficacy, panel is giving preference to time-limited therapies):
  - Fit patients: ibrutinib [I, A] (data for other BTKis for fit patients are still pending); CIT should be avoided due to survival disadvantage, but may be used if other options are not available [I, A]. Venetoclax plus obinutuzumab might be an alternative to BTKis, but data for fit patients are still pending [III, A].
  - Unfit patients: venetoclax plus obinutuzumab or ibrutinib or acalabrutinib [I, A] or chlorambucil plus obinutuzumab.
- CLL with mutated IGHV status and without *TP53* mutation or del(17p) (if there was similar efficacy, panel is giving preference to time-limited therapies):
  - Fit patients: CIT according to age (FCR or BR) or ibrutinib [I, A]. Venetoclax plus obinutuzumab might be an alternative to BTKis, but data for fit patients are still pending [III, A].
  - Unfit patients: venetoclax plus obinutuzumab [I, A] or chlorambucil plus obinutuzumab or ibrutinib or acalabrutinib [I, A].
- *TP53* mutation or del(17p): ibrutinib or acalabrutinib or venetoclax plus obinutuzumab or venetoclax alone or idelalisib plus rituximab [III, A].
- Early relapse: change of therapy to venetoclax plus rituximab or ibrutinib or acalabrutinib or another BTKi if approved and available [I, A].
- Late relapse and no del(17p) or *TP53* mutation: ibrutinib or venetoclax plus rituximab or repeat front-line therapy [II, B].
- Autoimmune cytopaenia should be treated with corticosteroids. In patients not responding to corticosteroids, treatment of CLL based on anti-CD20 antibodies or also BCRis should be considered [IV, A].
- Except after alloSCT, MRD measurement is not yet recommended as a clinical routine test [IV, C].

FOLLOW-UP, LONG-TERM IMPLICATIONS AND SURVIVORSHIP

At the present time, it is not clear if long-lasting remissions observed in a minority of patients after CIT or alloSCT as well as venetoclax-based combinations are equivalent to a functional cure in a proportion of patients. Therefore, life-long observation and follow-up is recommended for all patients. In totally asymptomatic patients, the follow-up should include a blood cell count and the palpation of LNs, liver and spleen every 3-12 months depending on the dynamics of the disease. Special attention should be paid to the appearance of autoimmune cytopaenia. Moreover, CLL patients have a twofold to sevenfold increased risk of developing secondary malignancies [mostly solid cancers, but also secondary MDS or acute myeloblastic leukaemia (AML)].

Richter's transformation

The transformation into a diffuse large B-cell lymphoma (DLBCL) occurs in 2%-15% of CLL patients during the course

of their disease, in particular after several lines of CIT. The diagnosis must be confirmed by a histopathology exam of an LN (biopsy or excision). A positron emission tomography (PET)-CT scan can be useful to guide biopsy [IV, C]. Richter's transformation into DLBCL usually has a poor prognosis, in particular if DLBCL is clonally related to CLL and/or the patient has been exposed to prior CLL therapy. For this reason, it is strongly advised to define the clonal relation between DLBCL and CLL by comparing IGHV sequences. Treatment regimens for Richter's transformation include therapies used in DLBCL such as rituximab, cyclophosphamide, vincristine, doxorubicin and dexamethasone (R-CHOP). More intense treatment regimens such as rituximab, cyclophosphamide, vincristine, doxorubicin and dexamethasone alternating with methotrexate and cytarabine (R-hyperCVAD) or oxaliplatin, fludarabine, cytarabine and rituximab (OFAR) have not improved outcome and may cause considerable toxicity [IV, D]. If possible, these patients should enter into clinical trials.

Response duration of Richter's transformation is typically short, and alloSCT should be recommended to all patients with clonally-related Richter's transformation with an available donor and sufficient fitness [IV, B].[78] In patients unsuitable for alloSCT, autoSCT can be considered.[79] If the CLL and DLBCL are clonally unrelated because of different Ig gene rearrangements, the disease should be treated as a *de novo* DLBCL because the DLBCL is a second malignancy (i.e. R-CHOP as first-line, reserving stem cell transplantation for cases not responding or relapsing after R-CHOP).[78]

The transformation of CLL into Hodgkin lymphoma (HL) represents a separate entity, though it is included in the term Richter's transformation. Here, conventional ChT against HL often achieves long-lasting remissions.[78]

Recommendations

- The transformation into DLBCL occurs in 2%-15% of CLL patients during the course of their disease, in particular after several lines of CIT. The diagnosis of transformation must be confirmed by histopathology exam of an LN (biopsy or excision). A PET-CT scan can be useful to guide biopsy [IV, C].
- Response duration of Richter's transformation is typically short, and alloSCT should be recommended to all patients with clonally-related Richter's transformation with an available donor and sufficient fitness [IV, B].
- In clonally unrelated disease, DLBCL should be treated as a *de novo* DLBCL.
- Transformation of CLL into the HL variant should be treated with conventional ChT against HL.

METHODOLOGY

These Clinical Practice Guidelines were developed in accordance with the ESMO standard operating procedures for Clinical Practice Guidelines development (http://www.esmo.org/Guidelines/ESMO-Guidelines-Methodology). 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 Supplementary Table S1, available at https://doi.org/10.1016/j.annonc.2020.09.019.[80] 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.

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