Treatment in patients with CLL

Criteria for treatment initiation

Includes best practice sharing by
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Therapy for CLL[1,2]

- Only patients with active or symptomatic disease, or with advanced Binet or Rai stages require therapy
- When treatment is indicated, several therapeutic options exist
- At relapse, the initial treatment may be repeated if the treatment-free interval exceeds 3 years
- If the disease relapses earlier, therapy should be changed using an alternative regimen
- Patients with a del(17p) or *TP53* mutation are usually resistant to chemotherapy and should therefore be treated with targeted agents

iwCLL guideline recommendations regarding indications for treatment in CLL[2]

	General practice*	Clinical trial
Treat with Rai low-risk group	NGI†	RQ
Treat with Binet stage A	NGI†	RQ
Treat with Binet stage B or Rai intermediate-risk group	Possible†	Possible†
Treat with Binet stage C or Rai high-risk group‡	Yes	Yes
Treatment of active/progressive disease	Yes	Yes
Treat without active/progressive disease	No	RQ

Goals for CLL therapy[3]

As CLL remains an incurable disease in most cases, the goals of therapy are to:

Improve quality of life

Prolong survival

In daily life, important treatment endpoints in clinical trials, such as response rate, MRD status or PFS, may be more relevant for young and/or fit patients than in older patients and/or patients with a relevant comorbidity

Ultimately, in most patients, survival depends on the effect and choice of treatment sequences given along the course of the disease

Criteria to define symptomatic or active disease[2,3]

iwCLL guideline criteria

1. Evidence of progressive marrow failure as manifested by the development of, or worsening of, anaemia and/or thrombocytopenia. Cut-off levels of Hb <10g/dL or platelet counts of <100,000/µL are generally regarded as indication for treatment§
2. Massive (ie, ≥6cm below the left costal margin), progressive or symptomatic splenomegaly
3. Massive (ie, ≥10cm in longest diameter), progressive or symptomatic lymphadenopathy
4. Progressive lymphocytosis with an increase of ≥50% over a 2-month period, or LDT of less than 6 months
   - LDT can be obtained by linear regression extrapolation of ALC obtained at intervals of 2 weeks over an observation period of 2–3 months; patients with initial blood lymphocyte counts of <30,000/µL may require a longer observation period to determine the LDT

   Factors contributing to lymphocytosis other than CLL (eg, infections, steroid administration) should be excluded
5. Autoimmune complications including anaemia or thrombocytopenia are poorly responsive to corticosteroids
6. Symptomatic or functional extranodal involvement (eg, skin, kidney, lung, spine)
7. Disease-related symptoms as defined by any of the following:
   - (a) Unintentional weight loss ≥10% within the previous 6 months
   - (b) Significant fatigue (ie, ECOG PS 2 or worse, cannot work or unable to perform usual activities)
   - (c) Fevers ≥100.5°F or 38.0°C for 2 or more weeks without evidence of infection
   - (d) Night sweats for ≥1 month without evidence of infection

Factors contributing to these symptoms other than CLL (eg, secondary neoplasia, infections, sleep disorders, anxiety, menopause) should be excluded, particularly when any of these symptoms are the only criterion to start therapy.[3]

ALC, absolute lymphocyte counts; CLL, chronic lymphocytic leukaemia; del (17p), deletion of 17p; ECOG PS, Eastern Cooperative Oncology Group Performance Status; Hb, haemoglobin; iwCLL, International Workshop on Chronic Lymphocytic Leukemia; LDT, lymphocyte doubling time; MRD, minimal residual disease; NGI, not generally indicated; PFS, progression-free survival; RQ, research question; *TP53*, tumour protein 53

*General practice is defined as the use of accepted treatment options for a CLL patient not enrolled on a clinical trial. Early therapy of CLL is generally not recommended outside of clinical trials. However, we recognise the need to conduct clinical trials testing the early use of novel agents; †Treatment is indicated if the disease is active; ‡Anaemia and/or thrombocytopenia from CLL-unrelated causes should be excluded; §However, it should be pointed out that in some patients, platelet counts of <100 000/µL may remain stable over a long period of time but this situation does not automatically require therapeutic intervention

1. Hallek M, Al-Sawaf O. Am J Hematol 2021;96:1679–1705; 2. Hallek M, et al. Blood 2018;131:2745–60; 3. Eichhorst B, et al. Ann Oncol 2021;32:23–33

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Investigations prior to treatment

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The different CLL-IPI categories:[1]

The CLL-IPI separates 4 groups with different survival at 5 years:

CLL-IPI category	OS at 5 years	Potential clinical consequence
Low risk	93.2%	Do not treat
Intermediate risk	79.3%	Do not treat except if the disease is really symptomatic
High risk	63.3%	Treatment is indicated except if the disease is asymptomatic
Very high risk	23.3%	If you need to treat, use targeted therapy or enrolment into a clinical trial

Investigations prior to treating patients with CLL[2]

Test	Details
Assessment before treatment	
· History and physical, performance status	Always
· CBC and differential count	Always
· Marrow aspirate and biopsy	WCI*
· Serum chemistry, serum immunoglobulin, and direct antiglobulin test	Always
· Chest radiograph	Always
· Infectious disease status	Always
Additional tests before treatment	
· Molecular cytogenetics (FISH) for del(13q), del(11q), del(17p), add (12) in peripheral blood lymphocytes	Always
· Conventional karyotyping in peripheral blood lymphocytes (with specific stimulation)	NGI†
· *TP53* mutation	Always
· *IGHV* mutational status	Always
· Serum β2-microglobulin	Des
· CT scan of chest, abdomen and pelvis	NGI
· MRI and PET scans	NGI
· Abdominal ultrasound‡	Poss

Biomarker testing in CLL[3]

- Biomarker testing results are prognostic and may be predictive for informing treatment decisions for individual patients
- Critical results from interphase FISH testing for del(17p), del(11q), del(13q) and trisomy 12, and sequencing for mutations in *TP53* and *IGHV* somatic hypermutation status inform a patient's risk stratification and their potential response to CLL therapies
- The value of testing has been increasingly recognised, with prognostic models and diagnostic guidelines recommending to include it when making treatment considerations

CLL-IPI is the most relevant prognostic score[1]

CLL-IPI uses a weighted grading of 5 independent prognostic factors:

- *TP53* deletion and/or mutation
- *IGHV* mutational status
- Serum β2-microglobulin
- Clinical stage
- Age

Test before treating CLL[3–5]

Predictive and prognostic testing are critical before choosing any therapy for CLL:

- **Prognostic markers** help predict the likely outcome of cancer for a group, but less so for any particular individual
- **Predictive markers** help predict the likelihood of benefiting from specific therapies

CLL is very heterogeneous in how it behaves, its ability to resist certain therapies and its sensitivity to others will be critical in tailoring the appropriate therapy.

Most prognostic and predictive factors can change over time, so it is important to retest before starting treatment, even if you tested at diagnosis or after the last treatment as CLL can evolve over time.

Tests before treatment[2,4]

Test	Details
	A FISH test looks for common chromosomal abnormalities that predict the likelihood that various CLL treatments will be effective and durable, eg, if FISH testing finds a del(17p), traditional CIT will not be effective and should be avoided
	It is important to test *IGHV* (also called *IgVH*) mutation status, which almost never changes over time, so it is generally not recommended that it be retested. Patients with a 'mutated' *IGHV* immunoglobulin do much better with traditional CIT than those who are unmutated
	*TP53* is the gene on the short arm of the 17th chromosome that helps chemotherapy to work and suppress cancer growth. It has been called the 'guardian of the genome' because it tries to repair damaged genetic material in the CLL cells. If it can't repair what's broken by chemotherapy or any other cause, it signals the cell to commit programmed cell death or apoptosis. If del(17p) is missing or mutated, generally chemotherapy will not work and the CLL can be harder to manage

Test	Del(17p)	*TP53*	*IGHV*
Test before first treatment	✓	✓	✓
Test before every treatment	✓	✓	X

CBC, complete blood count; CIT, chemoimmunotherapy; CLL, chronic lymphocytic leukaemia; CT, computed tomography; del, chromosome deletion; Des, desirable; FISH, fluorescence in situ hybridisation; *IGHV*, immunoglobulin heavy chain variable; IPI, International Prognostic Index; MRI, magnetic resonance imaging; NGI, not generally indicated; PET, positron emission tomography; OS, overall survival; Poss, possible; *TP53*, tumour protein 53; WCI, when clinically indicated
*Unclear cytopenia; †Conventional karyotyping in peripheral blood lymphocytes (with specific stimulation) may be useful before therapy, if established methodology is available; ‡Used in some countries to monitor lymphadenopathy and organomegaly

1. Hallek M, Al-Sawaf O. Am J Hematol 2021;96:1679–1705; 2. Hallek M, et al. Blood 2018;131:2745–60; 3. Mato AR, et al. Clin Lymphoma Myeloma Leuk 2020;20:174–83.e3; 4. CLL Society. Test before treat. https://cllsociety.org/newly-diagnosed/test-before-treat/. Accessed 9 January 2023; 5. National Comprehensive Cancer Network®. Distress during cancer care. 2020. https://www.nccn.org/patients/guidelines/content/PDF/distress-patient.pdf. Accessed 9 January 2023

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