Managing a CLL relapse

Criteria for treatment initiation

Includes best practice sharing by
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CLL relapse[1]

Unfortunately, CLL is a disease that has no cure and relapse is inevitable in most patients with time. However, positive treatment advances mean that remission periods are now longer in duration.[1]

Continuous treatments can cause most patients to progress while on treatment and therefore monitoring for progressive disease is essential.[1,2]

Relapse is defined as evidence of disease progression in a patient who has previously achieved a CR or PR for ≥6 months.[2]

iwCLL criteria to define progressive disease[2]

Progressive disease (PD) during or after therapy is characterised by at least one of the following, when compared with nadir values:

1. **Lymphadenopathy* – disease progression occurs if one of the following events is observed:**
   - Appearance of any new lesion such as enlarged lymph nodes (≥1.5cm), splenomegaly, hepatomegaly, or other organ infiltrates – *transient increases of lymph node size during treatment with novel inhibitors may occur and should not be counted as PD*
   - An increase by ≥50% in greatest determined diameter of any previous site (≥1.5cm)
2. An increase in the spleen size by ≥50% or the de novo appearance of splenomegaly†
3. An increase in the liver size of ≥50% of the extent enlargement of the liver below the costal margin defined by palpation, or the de novo appearance of hepatomegaly‡
4. An increase in the number of blood lymphocytes by 50% or more with at least 5 x 10^9/L B lymphocytes§
5. Transformation to a more aggressive histology (Richter's syndrome or Richter's transformation)||
6. Occurrence of cytopenia (neutropenia, anaemia, or thrombocytopenia) directly attributable to CLL and unrelated to autoimmune cytopenias:
   - **During therapy**: Cytopenias may occur as a side effect of many therapies and should be assessed according to the **Grading Scale for Haematological Toxicity** table (please see on the right)
   - **Post-treatment:** The progression of any cytopenia (unrelated to autoimmune cytopenia), as documented by a decrease of Hb levels ≥2g/dL or <10g/dL, or by a decrease of platelet counts ≥50% or <100 x 10^9/L, which occurs at least 3 months after treatment, defines disease progression if the marrow biopsy is consistent with the cytopenia resulting from increased marrow infiltration of clonal CLL cells, and is not considered a treatment-related toxicity

Genetic prognostic markers[1]

The two most important CLL genetic prognostic markers that significantly affect the course of the disease and the likelihood of relapse are:

- **del(17p) which occurs in 30% of patients who experience a relapse**
- ***TP53* mutations and/or no *IGHV* mutation**

Treating relapsed CLL[3]

Poorer treatment responses, as well as shorter time interval before relapse associated with the **del(17p)** mutation, ***TP53*** mutation and the lack of mutated ***IGHV*** are the focus for using new targeted therapies to treat CLL.[1]

iwCLL guideline grading scale for haematological toxicity in CLL[2]

Grade¶	Decrease in platelets# or Hb** (nadir) from baseline value (%)	Absolute neutrophil count (nadir)** x 10^9/L
0	No change to 10	≥2
1	11–24	≥1 and <2
2	25–49	≥1 and <1
3	50–74	≥0.5 and <1
4	≥75	<0.5

Goals of CLL therapy[3,4]

Since CLL remains, in most cases, an incurable disease, the goals of therapy are to:[3]

Improve quality of life

Prolong survival

It is important to realise that every person living with CLL is unique, and starting or changing treatment depends on many factors, only one of which is the iwCLL criteria. Treatment decisions are dependent upon the speed of progression and number of previous treatments.

Patient wishes and preferences need to be taken into account using a shared decision-making model.[4]

ANC, absolute neutrophil count; CLL, chronic lymphocytic leukaemia; CR, complete remission; CT, computed tomography; del, chromosome deletion; G-CSF, granulocyte-colony stimulating factor; Hb, haemoglobin; *IGHV*, immunoglobulin heavy chain variable; iwCLL, International Workshop on Chronic Lymphocytic Leukemia; PD, progressive disease; PR, partial remission; TP, tumour protein
*Progression of lymphadenopathy is often discovered by physical examination and should be recorded at regular intervals. In CLL, the use of imaging (CT scans) usually does not add much information for the detection of progression or relapse; †In the setting of splenomegaly, the splenic length must increase by ≥50% of the extent of its prior increase beyond baseline (eg, a 15-cm spleen must increase to ≥16cm). If no prior splenomegaly was observed at baseline or if splenomegaly has resolved with treatment, the spleen must increase by at least 2cm from baseline; ‡Given the impact of numerous medical conditions, liver size by physical examination or by CT scan is not a reliable measure of hepatic involvement by CLL and should only be counted if hepatomegaly is clearly attributable to lymphoid involvement; §Certain therapies (eg, kinase inhibitors) may cause lymphocytosis. In the setting of therapy with such agents, an increase in blood lymphocyte count by itself does not uniformly indicate an increased tumour burden but may reflect redistribution of leukaemia cells from lymphoid tissues to the blood. This should be predefined in the protocol of clinical trials for therapies in which redistribution of disease occurs. In such cases, increased lymphocytosis alone is not a sign of treatment failure or PD; ||The diagnosis of Richter's transformation should be established by lymph node or other tissue biopsy; ¶Grades: 1, mild; 2, moderate; 3, severe; 4, life-threatening; 5, fatal. Death occurring as a result of toxicity at any level of decrease from baseline will be recorded as grade 5; #Platelet counts must be below normal levels for grades 1–4. If, at any level of decrease the platelet count is <20 x 10^9/L, this will be considered grade 4 toxicity unless a severe or life-threatening decrease in the initial platelet count (eg, 20 x 10^9/L) was present at baseline, in which case the patient is not evaluable for toxicity referable to platelet counts; **Hb levels must be below normal levels for grades 1–4. Baseline and subsequent Hb determinations must be performed before any given transfusions. The use of erythropoietin is irrelevant for the grading of toxicity but should be documented; ††If the ANC reaches <1 x 10^9/L, it should be judged to be grade 3 toxicity. Other decreases in the white blood cell count or in circulating granulocytes are not to be considered because a decrease in the white blood cell count is a desired therapeutic endpoint. A gradual decrease in granulocytes is not a reliable index in CLL for stepwise grading of toxicity. If the ANC was <1 x 10^9/L before therapy, the patient is not evaluable for toxicity referable to the ANC. The use of G-CSF is irrelevant for the grading of toxicity but should be documented

1. Leukaemia Care. Relapse in chronic lymphocytic leukaemia (CLL). https://media.leukaemiacare.org.uk/wp-content/uploads/Relapse-in-Chronic-Lymphocytic-Leukaemia-CLL-Web-Version.pdf. Accessed 9 January 2023; 2. Hallek M, et al. Blood 2018;131:2745–60; 3. Eichhorst B, et al. Ann Oncol 2021;32:23–33; 4. NICE. Shared decision making. https://www.nice.org.uk/about/what-we-do/our-programmes/nice-guidance/nice-guidelines/shared-decision-making. Accessed 9 January 2023

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