Response assessment in patients with CLL

Overview of treatment response assessment

Response assessment for CLL[1,2]

Evaluating response to treatment of CLL is an important part of the treatment pathway. Treatment response categories can be separated into:

- Complete remission (CR)
- CR with incomplete marrow recovery (CRi)
- Partial remission (PR)
- Stable disease (SD)
- Progressive disease (PD)
- Refractory disease

The assessment of minimal residual disease (MRD) is an additional and increasingly important method of response assessment.

iwCLL definition of response in CLL[1-3]

Response category	Parameter

CR definition in general practice:
· Blood lymphocytes <4000/µL
· BM lymphoid cells ≤30%
CR definition in clinical trials:
· CT negative
· MRD assessment
· BM biopsy with IHC or flow cytometry
	CR requires all of the following criteria:
	· Peripheral blood lymphocytes (evaluated by blood and differential count) <4 x 10^9/L
	· Absence of significant lymphadenopathy by physical examination. In clinical trials, a CT scan of the neck, abdomen, pelvis and thorax is desirable if previously abnormal. Lymph nodes should be <1.5cm in longest diameter*
	· No splenomegaly or hepatomegaly by physical examination. In clinical trials, a CT scan of the abdomen should be performed at response assessment and should show no evidence for lymphadenopathy and splenomegaly†
	· Absence of disease-related constitutional symptoms
	· Blood counts need to show the following values:
	  · Neutrophils ≥1.5 x 10^9/L
	  · Platelets ≥100 x 10^9/L
	  · Hb ≥11.0g/dL (without RBC transfusions)

CRi	· Patients fulfil all the criteria for a CR but have persistent anaemia, thrombocytopaenia or neutropoenia
MRD	· MRD in CLL is defined as the number of leukaemic cells that can be detected in PB or BM following treatment. uMRD can be defined as the presence of less than 1 CLL cell in 10,000 leukocytes (<10–4), but this is not yet standardised‡[4]
PR or PD	· Refer to the **iwCLL Guideline response definition after treatment of CLL** table on the right
SD	· Patients who have not achieved a CR or a PR, and who have not exhibited PD, are considered to have stable disease (which is equivalent to a non-response)
Refractory disease	· Refractory disease is defined as treatment failure§ or as progression within 6 months from the last dose of therapy

iwCLL Guideline recommendations regarding the response assessment in CLL[2]

Diagnostic test	General practice‖	Clinical trial
Full patient history and physical examination	Always	Always
CBC and differential count	Always	Always
Marrow aspirate and biopsy	At cytopenia of uncertain cause	At CR or cytopenia of uncertain cause
Assessment for MRD	NGI	Desirable
Abdomen ultrasound¶	Possible, if previously abnormal	NGI
CT scans of chest, abdomen, and pelvis	NGI	Recommended if previously abnormal and otherwise with a CR and PR

iwCLL Guideline response definition after treatment of CLL[2]

Group	Parameter	CR	PR	PD	SD
A Assessing the lymphoid tumour load and constitutional symptoms	**Lymph nodes**	**None ≥1.5cm**	**Decrease ≥50% (from baseline)#**	**Increase ≥50% from baseline or from response**	**Change of -49% to +49%**
	Liver and/or spleen size**	Spleen size <13cm; liver size normal	Decrease ≥50% (from baseline)	Increase ≥50% from baseline or from response	Change of -49% to +49%
	Constitutional symptoms	**None**	**Any**	**Any**	**Any**
	Circulating lymphocyte count	Normal	Decrease ≥50% from baseline	Increase ≥50% over baseline	Change of -49% to +49%
B Assessing the haematopoietic system	**Platelet count**	**≥100 x 10^9/L**	**≥100 x 10^9/L or increase ≥50% over baseline**	**Decrease of ≥50% from baseline secondary to CLL**	**Change of -49% to +49%**
	Hb	≥11.0g/dL (untransfused and without erythropoietin)	≥11.0g/dL or increase ≥50% over baseline	Decrease of ≥2g/dL from baseline secondary to CLL	Increase <11.0g/dL or <50% over baseline, or decrease <2g/dL
	Marrow	**Normocellular, no CLL cells, no B-lymphoid nodules**	**Presence of CLL cells, or of B-lymphoid nodules, or not done**	**Increase of CLL cells by ≥50% on successive biopsies**	**No change in marrow infiltrate**

BM, bone marrow; CBC, complete blood count; CLL, chronic lymphocytic leukaemia; CR, complete remission; CRi, CR with incomplete marrow recovery; CT, computerised tomography; Hb, haemoglobin; IHC, immunohistochemistry; iwCLL, International Workshop on Chronic Lymphocytic Leukemia; MRD, minimal residual disease; NGI, not generally indicated; PB, peripheral blood; PD, progressive disease; PR, partial remission; RBC, red blood cell; SD, stable disease; uMRD, undetectable MRD

*Once this is determined, further imaging should not be required until disease progression is apparent by clinical examination or on blood testing; †Consensus response cut-off for splenomegaly of 13cm in craniocaudal length. However, the persistence of splenomegaly may not correlate with outcome. The quantitative determination of hepatomegaly seems more difficult and changes such as focal or disseminated hepatic nodules support liver involvement; ‡The sensitivity of the method used to evaluate for MRD should be reported, as should the tissue studied (blood or marrow). The proportion of patients achieving uMRD should be reported with the total number of patients treated with the specific therapy as the denominator (not as a proportion of responders or those in CR); §Responses that should be considered clinically beneficial include CR and PR and all others (eg, SD, non-response, PD, death from any cause) should be rated as a treatment failure; ‖General practice is defined as the use of accepted treatment options for a CLL patient not enrolled on a clinical trial; ¶Used in some countries to monitor lymphadenopathy and organomegaly. #Sum of the products of 6 or fewer lymph nodes (as evaluated by CT scans and physical examination in clinical trials or by physical examination in general practice); **Spleen size is considered normal if 13cm. There is not firmly established international consensus of the size of a normal liver; therefore, liver size should be evaluated by imaging and manual palpation in clinical trials and be recorded according to the definition used in a study protocol

1. Hallek M, Al-Sawaf O. Am J Hematol 2021;96:1679–1705; 2. Hallek M, et al. Blood 2018;131:2745–60; 3. Hallek M, et al. Blood 2008;111:5446–56; 4. Wierda WG, et al. Leukemia 2021;35:3059–72

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