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How to better understand iwCLL guidelines - CLL Response Assessment

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ABSTRACT

We use RECIST as a guideline for solid tumor trials and iRECIST as a guideline for cancer immunotherapy trials. Do you know what guidance we used for Mature B-Cell Malignancies? There are different guidelines for different Mature B-Cell Malignancies. Use the Lugano classification for non-Hodgkin lymphoma, the International Workshop on Waldenström macroglobulinemia(IWMM) guidelines for Waldenström's Macroglobulinemia(WM), and the International Workshop on Chronic Lymphocytic Leukemia (iwCLL) guidelines for chronic lymphocytic leukemia (CLL).

Chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) is the most common leukemia in the Western world, representing approximately 25% to 35% of all leukemias in the United States. In this paper, we will give some examples on how to use iwCLL guidelines for CLL analysis response assessment. And what is the difference between iwCLL 2008 and iwCLL2018. This paper will help you better understand iwCLL guidelines.

INTRODUCTION

Workshop on Chronic Lymphocytic Leukemia (iwCLL) published consensus guidelines for the design and conduct of clinical trials for patients with CLL that were revised from those previously published by the National Cancer Institute–sponsored Working Group. These guidelines provided definitions intended to standardize the assessment of patients that were adopted by the US Food and Drug Administration and European Medicines Agency for the evaluation of new drugs.

HISTORY OF IWCLL GUIDELINES

In 1988 and 1996, NCI-WG on CLL published guidelines for the design and conduct of CLL clinical trials to facilitate comparisons between different treatments and to establish definitions for studies. The US FDA adopted these guidelines in their evaluation and approval of new drugs. During the next decade, considerable progress was made in defining new prognostic markers, diagnostic parameters, and treatment options, prompting the iwCLL-sponsored Working Group to revise the 1996 criteria.

In 2008, the International Workshop on Chronic Lymphocytic Leukemia (iwCLL) published consensus guidelines for the design and conduct of clinical trials for patients with CLL that were revised from those previously published by the National Cancer Institute–sponsored Working Group. The previous edition of the consensus guidelines of the International Workshop on Chronic Lymphocytic Leukemia (iwCLL), published in 2008, has found broad acceptance by physicians and investigators caring for patients with CLL. The National Cancer Institute–Working Group 1996 guidelines were updated by the International Workshop on Chronic Lymphocytic Leukemia in 2008.

COMPARSION OF IWCLL2008 AND IWCLL2018 ON RESPONSE DEFINITION

Below shows main updated from iwCLL2008 to iwCLL2018 on response definition.

Group	Parameter	CR	PR	PD	SD
A	Lymph nodes	None ≥1.5 cm	Decrease ≥50% (from baseline)*	Increase ≥50% from baseline or from response	Change of −49% to +49%
	Liver and/or spleen size†	Spleen size <13 cm; 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	Platelet count	≥100 × 10⁹/L	≥100 × 10⁹/L or increase ≥50% over baseline	Decrease of ≥50% from baseline secondary to CLL	Change of −49 to +49%
	Hemoglobin	≥11.0 g/dL (untransfused and without erythropoietin)	≥11 g/dL or increase ≥50% over baseline	Decrease of ≥2 g/dL from baseline secondary to CLL	Increase <11.0 g/dL or <50% over baseline, or decrease <2 g/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

Figure 1 Main updated from iwCLL2008 to iwCLL2018 on response definition

The main updates from iwCLL2008 to iwCLL2018 that I have highlighted are: remove Marrow from Group A to Group B and add Constitutional symptoms to group A, remove Neutrophils from Group B.

For CR (complete remission), all of the criteria have to be met. For CR on Lymph node equal to 1.5cm, it can't be CR on the iwCLL2018, but on iwCLL2008 this criterion is OK. For spleen size, there are specific numerical definitions <13cm on iwCLL2018, but none for Splenomegaly on iwCLL2008. For CR Constitutional symptoms is none on iwCLL2018, and on iwCLL2008 there is no definition for this.

For PR (partial remission), at least 2 of the parameters of group A and 1 parameter of group B need to improve if previously abnormal; if only 1 parameter of both groups A and B is abnormal before therapy, only 1 needs to improve. For lymph nodes, liver and spleen on iwCLL2018 have definition decrease ⩾50% (from baseline), but on wiCLL2008 there is no 'from baseline' wording. And for group B Platelet count use greater than or equal to $100x10^9$/L on iwCLL2018 different from just greater than $100x10^9$/L on iwCLL2008.

For PD (progressive disease), at least 1 of the criteria of group A or group B has to be met. On iwCLL2018 for lymph nodes, liver and spleen increase ⩾50% from baseline or from response, but on iwCLL2008 there is no "from baseline or from response" wording. And for group B hemoglobin "decrease of ⩾2 g/dL from baseline secondary to CLL" on iwCLL2018, on iwCLL2008 there is no equal to 2 g/dL.

For SD (stable disease), all of the criteria have to be met; constitutional symptoms alone do not define PD. On iwCLL2018 add SD this is new add and wiCLL2008 does not have.

In iwCLL2018 sec 5.3.4 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 tumor burden but may reflect redistribution of leukemia 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. Please take care of this, and maybe need add PR-L on your response.

CLL ASSESSMENT OF RESPONSE: STEP BY STEP

There are two groups of parameters to review, A and B.

A parameters: Lymph nodes ("PPD and SPD"), Spleen, Liver, Constitutional symptoms, Circulating lymphocyte count.

B parameters: Platelet count, Hemoglobin, Marrow.

PPD = product of perpendicular diameters (single lymph node).

SPD= sum of PPDs of up to 6 target lymph nodes.

Example patient 1

	Baseline	Timepoint1
Lymph Node PPD LN1 (cm^2)	3.1*2.9 = 8.99	1.5*1.3 = 1.95

Lymph Node PPD LN2 (cm^2)	2.1*1.9=3.99	2.1*1.6 = 3.36
Lymph Node PPD LN3 (cm^2)	2*1.6=3.2	1.4*1.2 = 1.68
Lymph Node SPD (cm^2)	16.18	6.99
Lymphocytes (10^9/L)	15	30
Platelet count (10^9/L)	90	118

Table 1 Patient 1

Step 1. Calculate percentage change from baseline.

Percentage change from baseline SPD = (Current (6.99) - Baseline (16.18))/ Baseline (16.18) *100 = -0.57

Patient 1: With > 50% decrease in SPD (one 'A' parameter met).

Step 2. Look at lymphocytes.

If lymphocytes < $5*10^9$/L then +A.

If lymphocytes Decrease ≥ 50% then +A.

If Neither of the above then potential PRL.

If there is a >50% decrease in SPD and lymphocytes has 50% decrease from baseline (e.g. 16 to 8) then you have met "2A" parameters.

If lymphocytes is above 5, and not 50% decreased from baseline, then it is considered "lymphocytosis".

If you have 1A parameter (SPD reduced 50%) plus "lymphocytosis" it is tentatively considered a PRL, assuming the response meets at least 1 "B" parameter and does not meet definition of disease progression.

For Patient 1 from baseline lymphocytes =$15*10^9$/L to $30*10^9$/L then Lymphocytosis.

Step 3. Spleen/Liver.

Spleen: Decrease ≥ 50% or Abnormal => Normal then +A.

Liver: Decrease ≥ 50% or Abnormal => Normal then +A.

Patient 1: No hepatosplenomegaly at baseline.

Step 4. Ensure no PD.

Ensure the index lesions SPD has not increased by ⩾ 50% from nadir. Ensure no individual node > 1.5 cm has increased by ⩾ 50% in PPD from nadir. Single node progression is progressive disease (PD). Make sure that spleen/liver is not unequivocally increasing. Unequivocal increase in liver and/or spleen would be progressive disease (PD). Ensure no new lesions, no new cytopenia.

Patient 1: Confirmed no PD.

Step 5. Look at the "B" parameters (need to meet at least one B parameter for PR).

If Platelet count ⩾ 100 * 10^9/L then +B. If Hemoglobin ⩾ 11 g/dL then +B. if Marrow Presence of CLL cells, or of B-lymphoid nodules, or not done then +B. Or Platelet count, Hemoglobin increase ⩾ 50% over baseline.

Patient 1: Platelet count $118*10^9$/L then +B.

Step 6. Overall.

SPD = -57% +A.

lymphocytes = increased from baseline + lymphocytosis.

No hepato-splenomegaly.

No PD.

Platelet >$100*10^9$/L +B.

Patient1: 1A + 1B + lymphocytosis = PR with lymphocytosis.

Tips: The "B" parameters are different from A parameters in that we simply need at least one B parameter to be

above the required threshold. It does not matter which B parameter; it does not matter if that one B parameter was already above the threshold at baseline; it does not matter if other B parameters are getting 'worse' or going up and down.

Example Patient 2

	Baseline	Timepoint 1	Timepoint 2	Timepoint 3
Lymph Node PPD LN1 (cm^2)	3.1*2.9 = 8.99	3*2 = 6	2*1.5 = 3	0.8*0.6=0.48
Lymph Node PPD LN2 (cm^2)	4*6=24	2*1 = 2	1.1*0.5 = 0.55	1.1*0.5=0.55
Lymph Node SPD (cm^2)	32.99	8	3.55	1.03
Spleen (cm)	16.4	12.9	12.9	12.9
Liver	Normal	Normal	Normal	Normal
Lymphocytes (10^9/L)	20	90	9	3.5
Hemoglobin (g/dL)	11.6	12.3	13.6	14.1
Platelet count (10^9/L)	74	111	131	211
Absolute neutrophil count ($x10^9$/L)	824	1036	1115	2000

Table 2 Patient 2

Timepoint 1:

SPD: (-75.8%).

Lymphocytes: (+lymphocytosis).

Spleen (normalized), Liver (normal) (no evidence of progression).

B parameter (Hgb $\geqslant$11.0 g/dL and platelet $\geqslant 100*10^9$/L, B-parameters not worsening).

Response assessment: PR with lymphocytosis.

Timepoint 2:

SPD: (-89.2%).

Lymphocytes: (decreased from 20 to 9; $\geqslant$ 50% decrease).

Spleen (normalized), Liver (normal) (no evidence of progression).

B parameter (Hgb $\geqslant$11.0 g/dL and platelet $\geqslant 100*10^9$/L, B-parameters not worsening).

Response assessment: PR.

Timepoint 3:

SPD: (no LN>1.5cm).

Lymphocytes: (<4000).

Spleen (normalized), Liver (normal), no PD.

B parameter (Hgb $\geqslant$11.0 g/dL, platelet $\geqslant 100*10^9$/L, ANC> 1500).

If all A and B parameters meet CR then need Bone marrow confirm CR. Bone marrow < 30% lymphocytes, no lymphoid nodules.

Response assessment: CR.

Some patients fulfill all the criteria for a CR, but have a persistent anemia, thrombocytopenia, or neutropenia apparently unrelated to CLL, but related to drug toxicity. These patients should be considered as a different category of remission, CR with incomplete marrow recovery (CRi).

Some patients meet CR base on A and B parameters but when performing marrow biopsies in clinical trials, lymphoid nodules can be found that may reflect residual disease. These nodules may be recorded as nPR (nodular partial remission).

CONCLUSION

As a scientific programmer, better understanding iwCLL guidelines will help you derive a patient profile and understand what and why we derive these variables. This paper will help you better understand the response assessment on CLL. The examples presented in this paper are hypothetical and for illustrative purposes only.

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