National Cancer Institute–Sponsored Working Group Guidelines for Chronic Lymphocytic Leukemia: Revised Guidelines for Diagnosis and Treatment

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IN 1988, THE National Cancer Institute–sponsored Working Group (NCI-WG) on chronic lymphocytic leukemia (CLL) published guidelines for the design and conduct of clinical trials in CLL with two major objectives: first, to facilitate comparisons of results of clinical trials in CLL by providing standardized eligibility, response, and toxicity criteria; and, second, to encourage a framework on which to evaluate new scientific studies related to our increasing understanding of the biology and immunology of this disease.[1] These guidelines were rapidly adopted by the majority of the clinical trials community, and were also used by the Food and Drug Administration during its evaluation process for the approval of fludarabine. The differences between these guidelines and those subsequently published by the International Working Group on CLL (IWCLL), which were general-practice recommendations[2] are listed in Table 1. For diagnosis, the NCI-WG requires a lymphocyte count of 5×10^9/L, which is lower than the 10×10^9/L required by the IWCLL, unless the lymphocytes are B cells and the bone marrow is involved. To be considered a complete remission (CR), the NCI-WG criteria specify that less than 30% lymphocytes must be present in the bone marrow, with a recommendation that the clinical significance of lymphoid nodules be assessed prospectively (Table 1); the IWCLL allows focal infiltrates or nodules in the bone marrow aspirate and biopsy for CR. The IWCLL uses a shift in clinical stage as the sole index of partial remission (PR), whereas the NCI-WG provides more specific criteria and recommends validation of the relevance of stage shift. The major differences were the well-defined criteria in the NCI guidelines regarding when to initiate therapy, hematologic toxicity, and other important components for clinical trials design.

The purpose of this report is to present those revisions as considered necessary in view of advances in the past 8 years. Many of these revisions evolved as the guidelines were used in a systematic fashion in large clinical trials and, also, with the experience following the use of newer, more effective agents, such as fludarabine.[3-9] Although this report will focus on those changes recommended by the NCI-sponsored CLL Working Group, it will include sufficient details from the original guidelines so that the reader would find it a complete document by itself without having to refer to the older version.

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The initial NCI-WG Guidelines were primarily designed as recommendations for the conduct of clinical trials. An important addition is that these revisions will distinguish practice guidelines from research issues in the diagnosis, decision to treat, and monitoring response in patients with CLL (Table 2).

It is increasingly clear that a more biologically relevant staging and response assessment of patients is needed if we are to continue to make progress in defining clinically disparate patient subsets and generate more innovative and effective treatment options.

1. Diagnosis of B-CLL

1.1. *Peripheral Blood*

The clinical diagnosis of CLL requires an absolute lymphocytosis with a lower threshold of greater than 5,000 mature-appearing lymphocytes/μL in the peripheral blood, in part to separate CLL from small lymphocytic non-Hodgkin's lymphoma. Morphologically, the lymphocytes must appear mature. Nevertheless, it is common to find admixtures of larger or atypical cells, cells that are cleaved, as well as those consistent with prolymphocytes; however, the percentage that should be used to distinguish CLL from prolymphocytic leukemia (PLL) is controversial. A value of up to 55% is still consistent with the diagnosis of CLL.[10] The presence of greater than 55% prolymphocytes and/or greater than 15,000/μL of prolymphocytes establishes a diagnosis of primary PLL or progression to prolymphocytoid leukemia. However, the markers on these cells should be different (eg, PLL cells are negative for CD5 in half of the cases). Prospective assessment of the significance of the proportion of peripheral blood prolymphocytes, their phenotypic characteristics, and the patterns of clonal evolution remain important research questions. The peripheral blood should also be carefully examined to rule out a leukemic phase of mantle-cell lymphoma, another $CD5^+$ lymphoid malignancy.[11,12]

In the original guidelines,[1] a duration of lymphocytosis of at least 4 weeks was required to substantiate the diagnosis. Since the clinical features, histology, and phenotypic characteristics are sufficient to permit an accurate diagnosis of CLL in the majority of patients, only in rare patients with questionable or indolent/smoldering CLL is a reassessment of the lymphocyte count needed after $\geq$4 weeks.[13,14] The routine availability of peripheral blood lymphocyte immunophenotyping has facilitated the diagnosis of CLL in patients with a monoclonal lymphocytosis.[12,15,16] Three main phenotypic features define B-CLL: the predominant population shares B-cell markers (CD19, CD20, and CD23) with the CD5 antigen, in the absence of other pan–T-cell markers; the B cell is monoclonal with regard to expression of either κ or λ; and surface immunoglobulin (sIg) is of low density. Not only are these characteristics generally adequate for a precise diagnosis, but, importantly, they distinguish CLL from uncommon disorders such as PLL, hairy-cell leukemia, mantle-cell lymphoma, and other lymphomas.[12,15]

These guidelines have been proposed for B-CLL. There-

Table 1. Comparison of NCI-Working Group and IWCLL Guidelines for CLL

Variable	NCI	IWCLL
Diagnosis		
Lymphocytes ($\times 10^9$/L)	>5; ≥1 B-cell marker (CD19, CD20, CD23) + CD5	≥10 + B-phenotype or bone marrow involved <10 + both of above
Atypical cells (%) (eg, prolymphocytes)	<55	Not stated
Duration of lymphocytosis	None required	Not stated
Bone marrow lymphocytes (%)	≥30	>30
Staging	Modified Rai, correlate with Binet	IWCLL
Eligibility for trials	Active disease (details in document)	A: lymphs >50 $\times 10^9$/L doubling time <12 mo diffuse marrow B, C: all patients
Response criteria		
CR		
Physical exam	Normal	Normal
Symptoms	None	None
Lymphocytes ($\times 10^9$/L)	≤4	<4
Neutrophils ($\times 10^9$/L)	≥1.5	>1.5
Platelets ($\times 10^9$/L)	>100	>100
Hb (g/dL)	>11 (untransfused)	Not stated
Bone marrow lymphs (%)	<30; no nodules	Normal, allowing nodules or focal infiltrates
PR		
Physical exam (nodes, and/or liver, spleen)	≥50% decrease	Downshift in stage
Plus ≥1 of:		
Neutrophils ($\times 10^9$/L)	≥1.5	
Platelets ($\times 10^9$/L)	>100	
Hemoglobin (g/dL)	>11 or 50% improvement	
Duration of CR or PR	≥2 mo	Not stated
Progressive disease		Upshift in stage
Physical exam (nodes, liver, spleen)	≥50% increase or new	
Circulating lymphocytes	≥50% increase	
Other	Richter's syndrome	
Stable disease	All others	No change in stage

fore, the following lymphoid malignancies are specifically excluded from protocol studies directed at patients with B-CLL: T-CLL, prolymphocytic leukemia (B and T cell), hairy-cell leukemia and variant forms, splenic lymphoma with villous lymphocytes, large granular lymphocytosis, Sézary-cell leukemia, adult T-cell leukemia/lymphoma, and leukemic manifestations of non-Hodgkin's lymphomas, including follicular center-cell and mantle-cell lymphoma types.[12,15,17]

1.2. *Bone Marrow Examination*

A bone marrow aspirate and biopsy are generally not required to make the diagnosis of CLL. Nevertheless, CLL is a disease of the bone marrow, and it is appropriate to evaluate a major site of involvement. The aspirate smear must show ≥30% of all nucleated cells to be lymphoid. A bone marrow examination also provides useful prognostic information by determining whether there is diffuse or nondiffuse involvement,[18] and permits an assessment of the erythroid precursors and megakaryocytes.

1.3. *Immunophenotype*

As noted earlier, a thorough immunophenotypic profile of the malignant lymphocytes from the peripheral blood is necessary for the initial diagnosis of the patient with CLL.

1.4. *Molecular Biology/Cytogenetics*

Not only do cytogenetic analyses provide useful prognostic information, but they help identify potentially important nonrandom genetic alterations and oncogenes.[11,19-25] Sequential analysis of established genetic alterations may also be helpful in evaluating the evolution of the disease process. However, given the expense and limited availability of these studies, they should be restricted to a research setting in which to evaluate their potential prognostic and biologic importance.

2. Clinical Staging

We recognize that there are two somewhat different major staging methods that are currently in use throughout the world: the Rai system[26] and the Binet system.[27] In 1981, the IWCLL recommended that the two systems be integrated so that each of the Binet stages be subclassified with the Rai stage. However, the IWCLL-integrated system has not received widespread usage, and physicians continue to use either the Rai or Binet method in both patient care and in clinical trials. For clinicians using the Rai classification, we recommend the use of the modified version, which reduces the number of prognostic groups from five to three.[28] These two systems are outlined following.

2.1. *Rai System*

In the three-stage Rai system low risk encompasses Rai stage 0, with the clinical features of lymphocytosis in blood and bone marrow only. Intermediate risk encompasses stage

Table 2. Recommendations Regarding Evaluation and Monitoring of CLL Patients

Recommendation	General Practice*	Clinical Trial
Pretreatment evaluation		
History and physical	✓	✓
Examination of PBS	✓	✓
Immunophenotyping of PBLs	✓	✓
Bone marrow at diagnosis	+	✓
BM prior to therapy	✓¥	✓
Cytogenetic/molecular studies	X	*
CT scans, MRI, lymphangiogram gallium scan	X	X
Indications for treatment		
Treat with stage 0-1	X	*
Treat for active/progressive disease (newly dx)	✓	✓
Treat without active/progressive disease (newly dx)	X	*
Treat without active/progressive disease (relapsed/refractory)	X	*
Treat beyond maximum response	X	*
Response assessment		
CBC, differential	✓	✓
Bone marrow	+	✓
Phenotype	X	+
Cytogenetics/FISH	X	*

For purposes of this discussion, general practice is defined as the use of accepted treatment options for a CLL patient not enrolled on a clinical trial.

Abbreviations: ✓, always; X, not generally indicated; +, desirable; *, if a research question; ¥, if a study not performed recently, eg, at diagnosis; PBS, peripheral blood smear; PBLs, peripheral blood lymphocytes; dx, diagnosis; MRI, magnetic resonance imaging; FISH, fluorescence in situ hybridization.

I, with lymphocytosis and enlarged nodes, and stage II, with lymphocytosis plus splenomegaly and/or hepatomegaly (nodes positive or negative). High risk encompasses stage III, with lymphocytosis plus anemia, and stage IV, with lymphocytosis and thrombocytopenia.

2.2. *Binet Staging System*

Staging is based on the number of involved areas, and the level of hemoglobin (Hb) and platelet count. Whether significant adenopathy (>1 cm in diameter) is bilateral or unilateral is recorded.

Area of involvement considered for staging

(1) Head and neck, including the Wãldeyer ring (this counts as one area even if more than one group of nodes are enlarged).
(2) Axillae (involvement of both axillae counts as one area).
(3) Groins, including superficial femorals (involvement of both groins counts as one area).
(4) Palpable spleen.
(5) Palpable liver (clinically enlarged).

Stage A. Hb ≥10 g/dL and platelets ≥100 × 10^9/L and up to two of the above involved.

Stage B. Hb ≥10 g/dL and platelets ≥100 × 10^9/L and organomegaly greater than that defined for stage A, ie, three or more areas of nodal or organ enlargement.

Stage C. All patients, irrespective of organomegaly in whom Hb less than 10 g/dL and/or platelets less than 100 × 10^9/L.

3. Eligibility Criteria for Clinical Trials

3.1. *Clinical Stage*

The stage of CLL eligible for a clinical trial should reflect the therapeutic objectives, anticipated toxicities, and desired end results for each study. For example, a phase I study should involve only patients in advanced stages (Rai high risk, poor prognosis), while phase II and, particularly, phase III studies may also include patients in the intermediate-risk group. Decisions will be based on pilot data from phase I and early phase II trials with the particular agent or regimen. Patients with Rai stage 0 disease should generally not be entered into clinical trials. Other requirements for eligibility for clinical trials with respect to age, clinical stage, performance status, organ function, and status of disease activity should be defined for each study.

3.2. *Performance Status*

For phase I clinical trials, only patients with an Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0 to 2 should be eligible. For phase II and III clinical trials, patients with PS 0 to 3 may be eligible; however, these limits may be individualized on the basis of the drugs or therapies being tested. For trials in which it appears reasonable to include patients with PS 3, yet where there is a concern over the potential toxicities of an agent or therapy, it may be advisable to initially start those patients at a lower dose of the treatment (eg, 50% reduction) and to gradually increase the dose over subsequent courses to the standard dose, if the treatment is well tolerated and toxicity is within an acceptable range. This approach should be individualized for each relevant protocol and may not be appropriate for some therapies (eg, high-dose therapy with stem-cell support).

3.3. *Organ Function Eligibility for Clinical Trials*

Most chemotherapy agents possess the potential for toxicity to the liver, kidneys, heart, lungs, central or peripheral nervous system, or other organ systems. Therefore, organ function requirements must be guided by the known toxicities of each drug based on observations from animal studies and previous therapeutic trials. Normal function for organs for which there is a well-recognized, specific toxicity must be required. Otherwise, as a general principle:

3.3.1. Baseline liver enzymes (ie, transaminase levels) should be no worse than 1.5 times the upper range of normal values. Serum bilirubin concentration should be ≤2.0 mg/dL, unless resulting from documented hemolysis.

3.3.2. Baseline renal function (ie, blood urea nitrogen [BUN], creatinine) should be no worse than 1.5 times the upper range of normal values.

3.3.3. Baseline requirements for other studies (eg, systolic ejection fraction, pulmonary function tests) should be decided individually for each study.

3.4. *Infection Status*

3.4.1. Patients with active infections requiring systemic antibiotics should be excluded from B-CLL clinical trials until resolution of infection.

3.4.2. Patients who are human immunodeficiency virus

(HIV)-positive should be excluded because of their poor tolerance to chemotherapy and the potential risks from the immunosuppressive effects of new agents such as fludarabine.[29]

3.5. *Second Malignancies*

Patients with a second malignancy, other than non–basal-cell carcinoma of the skin or in situ carcinoma of the cervix, should not be entered onto a CLL clinical trial unless the tumor was treated with curative intent at least 2 years previously.

3.6. *Required Pretreatment Evaluation*

As already noted, the parameters that are considered necessary for a complete pretreatment evaluation differ whether the patient is being treated in a general practice setting or on a clinical research protocol (Table 2). In general, and where feasible, these studies should be quantified within 48 hours of placing a patient on a treatment protocol (except for bone marrow aspirate and biopsy) (see later), and computed tomography (CT) scans (see later). They should also be repeated at appropriate intervals to assess the maximum response to therapy.

3.61. Complete blood cell count (CBC; white blood cell count, hemoglobin and hematocrit, platelet count) and differential, including both percent and absolute number of lymphocytes and prolymphocytes, and reticulocyte count.

3.62. Unilateral bone marrow aspirate and biopsy should be performed within 2 weeks prior to entering the study, unless a previous diagnostic specimen was diffusely involved and there has been no intervening systemic therapy. It is preferable to evaluate the bone marrow at diagnosis for prognostic purposes; however, it is mandatory in clinical trials, and highly desirable in clinical practice, to perform a unilateral bone marrow aspirate and biopsy prior to treatment to provide a baseline for further response assessment. If a repeat bone marrow is obtained, it should be reviewed along with the original diagnostic sample.

3.63. Lymph node evaluation

3.531. Physical examination should record the diameter, in two planes, of the largest palpable nodes in each of the following sites: cervical, axillary, supraclavicular, inguinal, and femoral.

3.632. Chest radiograph.

3.633. CT scans are generally not necessary in the initial evaluation of patients with CLL, but should only be performed if clinically indicated. A chest CT may be useful if the chest radiograph shows hilar adenopathy. These should be obtained within 2 weeks prior to entering the protocol.

3.634. Lymph node biopsy is generally not indicated, unless such tissue is necessary for companion scientific studies.

3.64. Liver and spleen size should be assessed by physical examination. CT scans should only be performed if clinically indicated or if part of a research question (see section 3.433).

3.65. Serum chemistries (eg, creatinine, bilirubin).

3.66. Assessment of PS (ECOG).

3.67. Baseline immunobiologic, cytogenetic, and molecular assessment for CLL trials (see Table 2, and earlier). Those that should be performed on all patients include serum immunoglobulin determination, including quantitative immunoglobulins and immunoelectrophoresis, direct and indirect antiglobulin (Coombs' test), and immunophenotypic evaluation of the B-cell clone (see earlier).

4. Indications for Treatment

4.1. *Primary Treatment Decisions*

Once the diagnosis of CLL has been made, the treating physician is faced with the decision of not only how to treat the patient, but when to initiate therapy. Criteria for initiating treatment may be quite different between clinical practice and clinical trial conduct. A subset of patients are considered as having smoldering CLL; they include those with Rai stage 0 (Binet A), with a nondiffuse pattern of bone marrow involvement, a serum Hb concentration $\geq$13.0 g/dL, peripheral blood lymphocytes less than 30×10^9/L, and a lymphocyte doubling time longer than 12 months.[13,14] Therapy should not be offered to these patients until they exhibit clear evidence of disease progression. Other newly diagnosed patients with early stage disease (Rai 0 to I, Binet A), should be monitored without therapy until evidence of disease progression. Studies from both the French Cooperative Group on CLL and the Cancer and Leukemia Group B (CALGB) in patients with early-stage disease confirm that early therapy of patients with early-stage disease does not prolong survival,[30,31] but may be associated with an increased frequency of fatal epithelial cancers.[30] However, these studies were conducted with alkylator-based regimens, and the potential benefit of earlier therapy using nucleoside analog therapy is an important research question.

Whereas most patients with Rai stages III and IV require treatment at presentation, many can still be monitored without therapy until they exhibit evidence of progressive or symptomatic disease.

Active disease should be clearly documented for protocol therapy. The following criteria must be met:

(1) A minimum of any one of the following disease-related symptoms must be present:
   (a) Weight loss $\geq$10% within the previous 6 months.
   (b) Extreme fatigue (ie, ECOG PS 2 or worse; cannot work or unable to perform usual activities).
   (c) Fevers of greater than 100.5°F for $\geq$2 weeks without evidence of infection.
   (d) Night sweats without evidence of infection.
(2) Evidence of progressive marrow failure as manifested by the development of, or worsening of, anemia and/or thrombocytopenia
(3) Autoimmune anemia and/or thrombocytopenia poorly responsive to corticosteroid therapy
(4) Massive (ie, >6 cm below the left costal margin) or progressive splenomegaly
(5) Massive nodes or clusters (ie, >10 cm in longest diameter) or progressive lymphadenopathy
(6) Progressive lymphocytosis with an increase of >50% over a 2-month period, or an anticipated doubling time of less than 6 months
(7) Marked hypogammaglobulinemia or the development of a monoclonal protein in the absence of any of the above criteria for active disease is not sufficient for protocol therapy

Patients with CLL may present with a markedly elevated leukocyte count; however, the symptoms referable to leukocyte aggregates that develop in patients with acute leukemia rarely occur in patients with CLL. Therefore, the absolute lymphocyte count should not be used as the sole indicator for treatment, but should be included as a part of the total clinical picture, which includes the lymphocyte doubling time (see earlier).

4.2. *Second-Line Treatment Decisions*

Treatment of CLL is generally palliative in intent; therefore, patients who have relapsed may be followed without therapy until they experience disease-related symptoms or progressive disease, with deterioration of blood counts, discomfort from lymphadenopathy or hepatosplenomegaly, recurrent infections, or associated autoimmune disorders. A possible exception is allogeneic bone marrow transplantation. Recent data suggest that, in selected patients, allogeneic bone marrow transplantation or high-dose chemotherapy with autologous stem-cell support may be reasonable treatment options, particularly in the context of a clinical research protocol.[32-34]

The acceptable extent of prior therapy for protocol entry must be decided separately for each study.

(A) For all phase III therapeutic trials, it is recommended that only those patients who have not received previous cytotoxic or biological therapy be eligible. It is appropriate to include patients who have received previous corticosteroids if this is compatible with the therapeutic objectives of the trial. However, it may be necessary to analyze these previously treated patients as a separate group.

(B) For phase I and II studies, we recommend that no more than two types of prior therapy (eg, fludarabine, chlorambucil with or without prednisone) be allowed for entering patients. Certain trials may require previously untreated patients; this will be determined separately depending on the objectives of the study.

5. Definition of Response

Assessment of response should include a careful physical examination and evaluation of the peripheral blood and bone marrow. The response criteria in the original NCI-WG guidelines have been retained (Table 3).

5.1. Complete remission requires all of the following for a period of at least 2 months:

5.11. Absence of lymphadenopathy by physical examination and appropriate radiographic techniques.

5.12. No hepatomegaly or splenomegaly by physical examination, or appropriate radiographic techniques if in a clinical trial.

5.13. Absence of constitutional symptoms.

5.14. Normal CBC as exhibited by:

5.141. Polymorphonuclear leukocytes $\geq$ 1,500/μL.

5.142. Platelets > 100,000/μL.

5.143. Hemoglobin > 11.0 g/dL (untransfused).

5.15. Bone marrow aspirate and biopsy should be performed 2 months after clinical and laboratory results demonstrate that all of the requirements listed in 5.11 to 5.14 have been met to demonstrate that a CR has been achieved. The marrow sample must be at least normocellular for age, with less than 30% of nucleated cells being lymphocytes. Lymphoid nodules should be absent. If the bone marrow is hypocellular, a repeat determination should be made in 4 weeks. Samples should be re-reviewed in conjunction with the prior pathology.

Table 3. Grading Scale for Hematological Toxicity in CLL Studies

Decrease in Platelets* or Hb† (nadir) From Pretreatment value (%)	Grade‡	ANC/μL§ (nadir)
No change–		
10%	0	$\geq$2,000
11%–24%	1	$\geq$1,500 and <2,000
25%–49%	2	$\geq$1,000 and <1,500
50%–74%	3	$\geq$500 and <1,000
$\geq$75%	4	<500

* If, at any level of decrease the platelet count is <20,000/μL, this will be considered grade 4 toxicity, unless a severe or life-threatening decrease in the initial platelet count (eg, $\leq$20,000/μL) was present pretreatment, in which case the patient is inevaluable for toxicity referable to platelet counts.

† Baseline and subsequent Hb determinations must be performed before any given transfusions.

‡ 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 pretreatment will be recorded as grade V.

§ If the absolute neutrophil count (ANC) reaches less than 1,000/μL, 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, since a decrease in the white blood cell count is a desired therapeutic end point. A gradual decrease in granulocytes is not a reliable index in CLL for stepwise grading of toxicity. If the ANC was less than 1,000/μL prior to therapy, the patient is inevaluable for toxicity referable to the ANC.

5.16. For patients who fulfill all of the previous criteria for a CR, an abdominal CT scan may be performed to confirm this clinical and hematologic impression if clinically indicated or if required testing for a clinical research study.

5.2. PR is considered in a broad sense to enable the detection of agents with biological effect. To be considered a PR, the patient must exhibit 5.21 and 5.22 and/or 5.23 (if abnormal prior to therapy), as well as one or more of the remaining features for at least 2 months. In addition, the presence or absence of constitutional symptoms will also be recorded.

5.21. $\geq$50% decrease in peripheral blood lymphocyte count from the pretreatment baseline value.

5.22. $\geq$50% reduction in lymphadenopathy.

5.23. $\geq$50% reduction in the size of the liver and/or spleen.

5.24. Polymorphonuclear leukocytes $\geq$1,500/μL or 50% improvement over baseline.

5.25. Platelets >100,000/μL or 50% improvement over baseline.

5.26. Hemoglobin >11.0 g/dL or 50% improvement over baseline without transfusions.

5.27. In a subset of patients who are otherwise in a complete remission, bone marrow nodules can be identified histologically. It is, unfortunately, difficult with currently available techniques to determine the clonality of these nodules. The original NCI-WG guidelines suggested that patients with a CR and persistent nodules should be analyzed

carefully to compare their outcome relative to others who are more conventionally classified as a CR or PR.[1] Robertson et al[35] have since demonstrated that patients with a nodular CR had a shorter time to disease progression compared with patients with a CR. Therefore, nodular CRs should be reported separately from CRs, and should not be used to inflate the percentage of CRs. We recommend that they be referred to as nodular PRs (nPR) and included with the PRs.

5.28. A controversial issue is how best to categorize the response of patients who fulfill all the criteria for a CR, but who have a persistent anemia or thrombocytopenia apparently unrelated to disease activity and more likely the consequence of persistent drug toxicity. The long-term outcome of these patients may differ from the more routine complete responders. Therefore, these patients should not be considered CRs or a separate response category, but should be considered PRs. However, they should be monitored prospectively to better characterize their outcome, and may be described within the context of results of clinical trials.

5.3. Progressive disease will be characterized by at least one of the following:

5.31. ≥50% increase in the sum of the products of at least two lymph nodes on two consecutive determinations 2 weeks apart (at least one node must be ≥2 cm); appearance of new palpable lymph nodes.

5.32. ≥50% increase in the size of the liver and/or spleen as determined by measurement below the respective costal margin; appearance of palpable hepatomegaly or splenomegaly, which was not previously present.

5.33. ≥50% increase in the absolute number of circulating lymphocytes to at least 5,000/μL.

5.34. Transformation to a more aggressive histology (eg, Richter's syndrome or PLL with >55% prolymphocytes).

5.35. In the absence of progression, as defined earlier, the presence of a ≥2 g/dL decrease in Hb, or ≥50% decrease in platelet count, and/or absolute granulocyte count will not exclude a patient from continuing the study. Each protocol will define the amount of drug(s) to be administered with such hematological parameters. Bone marrow aspirate and biopsy are strongly encouraged to better define the cause of the suppressed counts.

5.4. Patients who have not achieved a CR or a PR, or who have not exhibited PD, will be considered to have stable disease.

5.5. Responses that should be considered clinically beneficial include CR, nPR and PR; all others, eg, stable disease, nonresponse, progressive disease, and death from any cause, should be rated as a treatment failure.

5.6. Because current criteria for response are arbitrary and often not validated by prospective studies, alternative criteria may also be evaluated; however, to ensure comparability with other studies, these should be studied within the framework of the current schema and be well defined, with adequate rationale. Should such a schema be determined to have important clinical relevance following prospective evaluation, it will be considered for incorporation into criteria for future studies.

5.7. Duration of response should be measured from the time the patient has exhibited the features of maximum response until evidence of progressive disease. Survival duration should be measured from the time of entry onto the clinical trial.

6. Prognostic Factors Requiring Stratification

6.1. Previous treatment versus no previous treatment in studies for which prior therapy is allowed.

6.2. If more than one clinical stage is allowed, patients should be stratified for stage (eg, if intermediate and poor risk are eligible, intermediate *v* poor), depending on the nature of the study and the available patient resources.

6.3. *Application of New Prognostic Factors*

In the interval since the initial publication of the guidelines, several modifications have been recommended.

6.31. Decrease in lymphocyte count: In several recent studies, a decrease in the peripheral blood lymphocyte count has been used as the primary index of response.[36] Although this parameter may identify a therapy that has lymphocytotoxic activity, there is no evidence that it has long-term clinical implications. It has, therefore, not been incorporated into the current response criteria.

6.32. Immunobiological assessment

6.321. Quantification of the serum immunoglobulin concentration in responders is recommended at the time of maximal clinical response, but it is not an established indicator of response.

6.322. Repeat immunophenotyping at the time of a response is not part of standard practice. Moreover, progression of disease after a CR should not be based purely on the basis of a small number of clonal cells identified using flow cytometric determinations.

6.323. In the clinical trials setting, not only should the peripheral blood smear and bone marrow aspirate and biopsy be carefully examined, but immunophenotype, cytogenetics, (including fluorescent in situ hybridization [FISH]), and molecular biologic studies provide important data and should be performed at diagnosis, at the time of maximal response, and at recurrence if part of a research question.

6.324. Serum β_2-microglobulin is recommended as an inexpensive prognostic marker.[37]

6.325. Other optional studies that may be of interest include markers of B-cell proliferation such as Ki-67, which might identify alterations in the malignant cell population, soluble CD23, adhesion molecules, or molecular analysis of specific genes (eg, oncogenes, tumor-suppressor genes). These scientific parameters that assess the biology of the malignant clone may help us to identify new therapeutic strategies.

6.33. Minimal residual disease: The optimal approach to the patient with minimal residual disease remains another important research issue. Careful assessment for minimal residual disease as determined by flow cytometry, cytogenetics, or similar studies is not indicated outside of a research study at the time of CR and at recurrence. Additional treatment decisions on the basis of minimal residual disease remains an issue for clinical investigation.

7. Assessment of Toxicity

An evaluation of potential treatment-induced toxicity in patients with advanced malignancies may be quite difficult, requiring careful consideration of both the manifestations of

the underlying disease, as well as adverse reactions to the therapies under study. Moreover, some of the conventional criteria for toxicity are not applicable to studies involving patients with hematological malignancies in general, or CLL in particular. An example is hematological toxicity; patients with advanced CLL may exhibit a deterioration in blood counts, which may represent either treatment-related toxicity or progressive bone marrow failure from the disease itself. This discrimination may become increasingly difficult as new agents are tested earlier in their development at a point where the complete spectrum of their toxicities has not yet been elaborated.

A few guidelines are presented recognizing that evaluation methods will be determined to a large extent within the therapy involved.

7.1. *Hematological Toxicity*

As is the case with virtually all of the hematological malignancies, an evaluation of hematological toxicity in patients with CLL must consider the high frequency of hematological compromise at the initiation of therapy. Therefore, the standard criteria used for solid tumors cannot be applied directly; many patients would be considered to have grade II to IV hematological toxicity at presentation.

Also, in the past, the peripheral blood neutrophil level has rarely been used as a criterion for dose modification since these values were felt to be unreliable in CLL. However, the increasing use of more effective therapeutic agents, particularly those with neutropenia as a dose-limiting toxicity (eg, nucleoside analogs), has resulted in clinically significant myelosuppression. Therefore, we have proposed a new dose-modification scheme for quantifying hematological deterioration in patients with CLL, which includes alterations in the dose of myelosuppressive agents based on the absolute neutrophil count (Table 3).

7.2. *Infectious Complications*

In CLL, as with many other hematological malignancies, it may be difficult to distinguish between the occurrence of infections related to the disease itself or to the consequences of therapy. However, such an analysis is of value when comparing the results of various treatments, particularly with immunosuppressive agents such as the nucleoside analogs.[29] The etiology of the infection should be reported and categorized as bacterial, viral, or fungal, and proven or probable. The severity of infections should be quantified as minor (requiring either oral antimicrobial therapy or symptomatic care alone), major (requiring hospitalization and systemic antimicrobial therapy), or fatal (death as a result of the infection).

7.3. *Nonhematological Toxicities*

Other nonhematological toxicities should be graded according to the NCI Common Toxicity Criteria.[38]

8. Reporting of Clinical Response Data

Clear and careful reporting of data is an essential part of any clinical trial. In clinical studies involving previously treated patients, patients who are relapsed or refractory should be clearly distinguished. Relapse is defined as a patient who has previously achieved the clinicopathologic criteria to be classified as a CR or PR, but, after a period of $\geq$6 months, demonstrated evidence of disease progression (Table 1). For those patients who have relapsed, it is also useful to describe the quality and duration of their prior response. Refractory disease refers to the clinical situation in which a patient fails to achieve at least a PR or progresses while on therapy.

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