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Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: a report from the International Workshop on Chronic Lymphocytic Leukemia updating the National Cancer Institute–Working Group 1996 guidelines

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Standardized criteria for diagnosis and response assessment are needed to interpret and compare clinical trials and for approval of new therapeutic agents by regulatory agencies. Therefore, a National Cancer Institute–sponsored Working Group (NCI-WG) on chronic lymphocytic leukemia (CLL) published guidelines for the design and conduct of clinical trials for patients with CLL in 1988, which were updated in 1996. During the past decade, considerable progress has been achieved in defining new prognostic markers, diagnostic parameters, and treatment options. This prompted the International Workshop on Chronic Lymphocytic Leukemia (IWCLL) to provide updated recommendations for the management of CLL in clinical trials and general practice. (Blood. 2008;111:5446-5456)

Introduction

In 1988 and 1996, a National Cancer Institute–sponsored Working Group (NCI-WG) on chronic lymphocytic leukemia (CLL) published guidelines for the design and conduct of clinical trials for patients with CLL to facilitate comparisons between different treatments and to establish definitions that could be used in scientific studies on the biology of this disease.[1,2] The US Food and Drug Administration also adopted these guidelines in their evaluation and approval of new drugs. During the past decade, considerable progress has been made in defining new prognostic markers, diagnostic parameters, and treatment options, prompting the IWCLL-sponsored Working Group to revise the 1996 criteria.

1. Diagnosis of CLL

The World Health Organization classification of hematopoietic neoplasias describes CLL as leukemic, lymphocytic lymphoma, being only distinguishable from small lymphocytic lymphoma (SLL) by its leukemic appearance.[3] In the World Health Organization classification, CLL is always a disease of neoplastic B cells, whereas the entity formerly described as T-CLL is now called T-cell prolymphocytic leukemia.[4]

It is important to verify that the patient has CLL and not some other lymphoproliferative disease that can masquerade as CLL, such as hairy cell leukemia, or leukemic manifestations of mantle cell lymphoma, marginal zone lymphoma, splenic marginal zone lymphoma with circulating villous lymphocytes, or follicular lymphoma. To achieve this, it is essential to evaluate the blood count, blood smear, and the immune phenotype of the circulating lymphoid cells (see sections 1.1 and 1.2).

1.1. Blood

The diagnosis of CLL requires the presence of at least 5×10^9 B lymphocytes/L (5000/μL) in the peripheral blood. The clonality of the circulating B lymphocytes needs to be confirmed by flow cytometry. The leukemia cells found in the blood smear are characteristically small, mature lymphocytes with a narrow border of cytoplasm and a dense nucleus lacking discernible nucleoli and having partially aggregated chromatin. These cells may be found admixed with larger or atypical cells, cleaved cells, or prolymphocytes, which may comprise up to 55% of the blood lymphocytes.[5] Finding prolymphocytes in excess of this percentage would favor a diagnosis of prolymphocytic leukemia (B-cell PLL). Gumprecht nuclear shadows, or smudge cells, found as cell debris, are other characteristic morphologic features found in CLL.

CLL or SLL might be suspected in otherwise healthy adults who have an absolute increase in the clonal B lymphocytes but who have less than 5×10^9/L B lymphocytes in the blood. However, in the absence of lymphadenopathy or organomegaly (as defined by physical examination or CT scans), cytopenias, or disease-related symptoms, the presence of fewer than 5×10^9 B lymphocytes per liter of blood is defined as "monoclonal B-lymphocytosis."[6] Monoclonal B-lymphocytosis may progress to frank CLL at a rate of 1% to 2% per year.[7]

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The definition of SLL requires the presence of lymphadenopathy and/or splenomegaly. Moreover, the number of B lymphocytes in the peripheral blood should not exceed 5×10^9/L. In SLL, the diagnosis should be confirmed by histopathologic evaluation of a lymph node biopsy whenever possible.

1.2. Immunophenotype

CLL cells coexpress the T-cell antigen CD5 and B-cell surface antigens CD19, CD20, and CD23. The levels of surface immunoglobulin, CD20, and CD79b are characteristically low compared with those found on normal B cells.[8,9] Each clone of leukemia cells is restricted to expression of either kappa or lambda immunoglobulin light chains.[8] Variations of the intensity of expression of these markers may exist and do not prevent inclusion of a patient in clinical trials for CLL.

In contrast, B-cell PLL cells do not express CD5 in half of the cases, and typically express high levels of CD20 and surface Ig.[10] In addition, the leukemia cells of mantle cell lymphoma, despite also expressing B-cell surface antigens and CD5, generally do not express CD23.

1.3. Other tests performed at diagnosis

The tests described in this section are not needed to establish the diagnosis of CLL but may help predict the prognosis or to assess the tumor burden. With the exception of molecular genetics fluorescence in situ hybridization (FISH), the application of these tests should not be used in routine practice to influence therapy and is not generally recommended. However, certain parameters, such as immunoglobulin mutational status, are useful for predicting the clinical course in individual cases. These tests can be recommended for patients who want a better prediction of the rate at which their disease might progress but it should be emphasized that the indication for treatment does not depend on any of these tests but on the clinical stage and the disease activity (see section 4).

1.3.1. Molecular cytogenetics. Using interphase FISH, cytogenetic lesions can be identified in more than 80% of all CLL cases.[11] The most common deletions are in the long arm of chromosome 13 [del(13q14.1)]. Additional frequent chromosomal aberrations include trisomy of chromosome 12, deletions in the long arm of chromosomes 11 [del(11q)] or 6 [del(6q)], or in the short arm of chromosome 17 [del(17p)].[11] When stimulated in vitro, CLL cells can have detectable chromosomal translocations, which are of potential prognostic significance.[12] Certain translocations can help distinguish other lymphoproliferative diseases from CLL (eg, t(11;14), which generally is found in mantle cell lymphoma).

There is increasing evidence from prospective clinical trials that detection of certain chromosomal deletions has prognostic significance. Patients with leukemia cells that have del(17p) have an inferior prognosis and appear relatively resistant to standard chemotherapy regimens using alkylating drugs and/or purine analogs.[13,14] In a retrospective analysis on several chromosomal aberrations detected by FISH, patients who had CLL cells with chromosomal aberrations del(11q) or del(17p) had an inferior outcome compared with patients who had leukemia cells with a normal karyotype or del(13q) as the sole genetic abnormality.[11] On the other hand, patients with leukemia cells having del(17p) may respond to therapy with alemtuzumab, either alone or in combination with other antileukemia agents.[15,16] Detection of these cytogenetic abnormalities has apparent prognostic value and may influence therapeutic decisions. For clinical trials, it is recommended that cytogenetics be performed before treating a patient on protocol. Additional genetic defects may be acquired during the course of the disease[17]; therefore, the repetition of FISH analyses seems justified before subsequent, second- or third-line treatment.

1.3.2. Mutational status of IgV_H, VH3.21 usage, and expression of ZAP-70 or CD38. The leukemia cells express immunoglobulin that may or may not have incurred somatic mutations in the immunoglobulin heavy chain variable region genes (IgV_H genes). The outcome of patients with leukemia cells that use an unmutated IgV_H gene is inferior to those patients with leukemia cells that use a mutated IgV_H gene.[18,19] In addition, the VH3.21 gene usage is an unfavorable prognostic marker independent of the IgV_H mutational status.[20] Leukemia-cell expression of ZAP-70 or CD38 was found to correlate with the expression of unmutated IgV_H genes and to predict a poor prognosis.[18,21-27] However, the association between expression of ZAP-70 or CD38 with the expression of unmutated IgV_H genes is not absolute. It is uncertain whether leukemia-cell expression of unmutated IgV_H genes or ZAP-70 predict the response to treatment or overall survival, once therapy is required.[14,28] Taken together, further clinical trials are needed to standardize the assessment of these parameters and to determine whether they should affect the management of patients with CLL.

1.3.3. Serum markers. Several studies have found that serum markers CD23, thymidine kinase, and β_2-microglobulin may predict survival or progression-free survival.[29-35] Assays for these markers should be standardized and used in prospective clinical trials to validate their relative value to the management of patients with CLL.

1.3.4. Marrow examination. In CLL, characteristically more than 30% of the nucleated cells in the aspirate are lymphoid. Although the type of marrow infiltration (diffuse vs nondiffuse) reflects the tumor burden and provides some prognostic information, recent results suggest that the prognostic value of BM biopsy may now be superseded by new prognostic markers.[36]

A marrow aspirate and biopsy generally are not required for the diagnosis of CLL. However, a marrow biopsy and aspirate can help evaluate for factors that might contribute to cytopenias (anemia, thrombocytopenia) that may or may not be directly related to leukemia-cell infiltration of the marrow. Because such factors could influence the susceptibility to drug-induced cytopenias, a marrow biopsy is recommended before initiating therapy. It is recommended to repeat a marrow biopsy in patients with persisting cytopenia after treatment to uncover disease- versus therapy-related causes.

2. Clinical staging

There are 2 widely accepted staging methods for use in both patient care and clinical trials: the Rai system[37] and the Binet system.[38] The original Rai classification was modified to reduce the number of prognostic groups from 5 to 3.[39] As such, both systems now describe 3 major subgroups with discrete clinical outcomes. These 2 staging systems are simple, inexpensive, and can be applied by physicians worldwide. Both rely solely on a physical examination and standard laboratory tests and do not require ultrasound, computed tomography (CT), or magnetic resonance imaging. These 2 systems are outlined in the following 2 sections.

2.1. Rai staging system

The modified Rai classification defines low-risk disease as patients who have lymphocytosis with leukemia cells in the blood and/or

marrow (lymphoid cells >30%; formerly considered Rai stage 0). Patients with lymphocytosis, enlarged nodes in any site, and splenomegaly and/or hepatomegaly (lymph nodes being palpable or not) are defined as having intermediate-risk disease (formerly considered Rai stage I or stage II). High-risk disease includes patients with disease-related anemia (as defined by a hemoglobin [Hb] level <110 g/L [11 g/dL]; formerly stage III) or thrombocytopenia (as defined by a platelet count $<100 \times 10^9$/L; formerly stage IV).

2.2. Binet staging system

Staging is based on the number of involved areas, as defined by the presence of enlarged lymph nodes of greater than 1 cm in diameter or organomegaly, and on whether there is anemia or thrombocytopenia.

Areas of involvement considered for staging

1. Head and neck, including the Waldeyer ring (this counts as one area, even if more than one group of nodes is 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 100 g/L (10 g/dL) or more and platelets 100×10^9/L or more and up to 2 of the above involved.

Stage B. Hb 100 g/L (10 g/dL) or more and platelets 100×10^9/L or more and organomegaly greater than that defined for stage A (ie, 3 or more areas of nodal or organ enlargement).

Stage C. All patients who have Hb less than 100 g/L (10 g/dL) and/or a platelet count less than 100×10^9/L, irrespective of organomegaly.

3. Eligibility criteria for clinical trials

The selection of CLL patients for clinical trials is similar to that for patients with other malignancies. Phase 1 or 2 clinical trials commonly, although not invariably, are intended for patients who have had prior therapy. It may be worth considering the inclusion of patients with SLL in some phase 1 or 2 trials exploring new agents in CLL. However, for SLL the response assessment should be done according to the lymphoma guidelines. The combination of new agents with standard therapy as part of phase 2 studies may be investigated in both untreated and previously treated patients. Phase 3 clinical trials are used to compare the clinical outcome using new treatment modalities with that using current standard therapy. Other requirements for eligibility with respect to age, clinical stage, performance status, organ function, or status of disease activity should be defined for each study.

3.1. Performance status and fitness

Before inclusion in a trial, the performance status as defined by the Eastern Cooperative Oncology Group (ECOG) should be 0 to 3. Future clinical trials involving elderly patients ideally should assess the comorbidity (fitness) and/or functional activity of patients (eg, such as that defined by "cumulative illness rating scale" or the "Charlson" score).[40,41]

3.2. Organ function eligibility for clinical trials

Most chemotherapy agents have potential toxicity for the liver, kidneys, heart, lungs, nervous system, or other organ systems. Therefore, organ function requirements should be guided by the known or suspected toxicity of each agent based on preclinical studies or prior clinical studies. Patients enrolled on protocols evaluating agents with known or suspected toxicity for a given organ(s) should have documented the specific organ function before therapy.

3.3. Infectious disease status

The status of specific infectious diseases as outlined in section 3.5 should be documented. Patients with active infections requiring systemic antibiotics or antifungal or antiviral drugs should have their infection resolved before initiating therapy in a clinical trial.

3.4. Second malignancies

Patients with a second malignancy, other than basal cell carcinoma of the skin or in situ carcinoma of the cervix or the breast, generally are not considered candidates for entry into clinical trials unless the tumor was successfully treated with curative intent at least 2 years before trial entry.

3.5. Required pretreatment evaluation

Parameters considered necessary for a complete pretreatment evaluation may differ depending on whether or not the patient is treated in a clinical protocol. Therefore, a clear distinction is made in sections 3.5 and 5 between recommendations for general practice and the requirements for clinical trials (Tables 1-3). If not indicated otherwise, recommendations are identical for clinical trials and general practice. In general, studies for defining these parameters should be performed within 2 weeks of clinical trial enrollment (except for marrow aspirate and biopsy and CT scans; see sections 3.5.1 and 3.5.1.2).

3.5.1. Essential pretreatment tests

3.5.1.1. Physical examination. The bidimensional diameters of the largest palpable lymph nodes in each of the following sites should be recorded: cervical, axillary, supraclavicular, inguinal, and femoral (Table 1). The size of the liver and spleen, as assessed by palpation, should also be recorded.

3.5.1.2. Assessment of performance status

3.5.1.3. A complete blood cell count. White blood cell count, hemoglobin and hematocrit, platelet count, and differential count, including both percent and absolute number of lymphocytes, and reticulocyte count should be performed. Reporting the proportion of prolymphocytes is desirable when these are present.

3.5.1.4. Marrow biopsy. Before initiating treatment in a clinical trial with potentially myelosuppressive agents, patients should undergo a unilateral marrow aspirate and biopsy. Repeat marrow biopsies may be compared with the pretreatment marrow specimen.

3.5.1.5. Serum chemistry. For example, creatinine, bilirubin, lactic dehydrogenase, transaminases, alkaline phosphatase.

3.5.1.6. Serum immunoglobulin levels.

3.5.1.7. Direct antiglobulin test.

3.5.1.8. Chest radiograph (when a CT scan is not performed).

3.5.1.9. Human immunodeficiency virus (HIV). Patients who are infected with HIV should be given special consideration because of the potential risks for immune suppression with most antileukemia therapies and the potential for compounded myelotoxicity of treatment with antiretroviral therapy.

Table 1. Pretreatment evaluation of patients with CLL

Diagnostic test	Section of guidelines	General practice*	Clinical trial
Tests to establish the diagnosis	1		
Complete blood count and differential count	1.1	Always	Always
Immunophenotyping of lymphocytes	1.2	Always	Always
Assessment before treatment	3.5.1		
History and physical, performance status	3.5.1.1, 3.5.1.2	Always	Always
Complete blood count and differential	3.5.1.3	Always	Always
Marrow aspirate and biopsy	3.5.1.4	Desirable	Desirable
Serum chemistry, serum immunoglobulin, direct antiglobulin test	3.5.1.5, 3.5.1.6, 3.5.1.7	Always	Always
Chest radiograph	3.5.1.8	Always	Always
Infectious disease status	3.3	Always	Always
Additional tests before treatment	3.5.2		
Cytogenetics (FISH) for del(13q), del(11q), del(17p), trisomy 12, del(6q) in the peripheral blood lymphocytes	3.5.2.1	Desirable	Always
IgVH mutational status, ZAP-70, and CD38	1.2	NGI	Always
CT scan of chest, abdomen, and pelvis	3.5.2.2	NGI	Desirable
MRI, lymphangiogram, gallium scan, PET scans	3.5.2.3	NGI	NGI
Abdominal ultrasound*	3.5.2.4	Possible	NGI

General practice is defined as the use of accepted treatment options for a patient with CLL who is not enrolled in a clinical trial.

NGI indicates not generally indicated; RQ, research question; PBS, peripheral blood smear; MRI, magnetic resonance imaging; PET, positron emission tomography; and FISH, fluorescence in situ hybridization.

*Used in some countries to monitor lymphadenopathy and organomegaly.

3.5.1.10. Cytomegalovirus (CMV). Therapies associated with the potential for reactivation of infection with CMV, such as alemtuzumab or allogeneic stem cell transplantation, should include plans for monitoring for active CMV disease and/or for providing anti-CMV therapy.[42] These should cover screening or early diagnosis of CMV reactivation and its subsequent management. However, a positive CMV serology does not represent a contraindication for alemtuzumab treatment or allogeneic stem cell transplantation. As a general recommendation for patients treated with alemtuzumab, close monitoring and/or therapy for active CMV disease should be considered for patients found to have evidence for increased levels of CMV in the blood by the polymerase chain reaction (PCR), even in the absence of clinical symptoms. In addition, evaluation and therapy for CMV is recommended for any patient with clinical symptoms of active CMV infection.

3.5.1.11. Hepatitis B and hepatitis C. Before initiating treatment, the evaluation for infection with hepatitis B virus (HBV) and hepatitis C virus (HCV) is recommended because reactivation of HBV and HCV infections may occur under therapy with immunosuppressive or myelosuppressive drugs. Chronic HBV carriers as defined by positive surface antigen undergoing chemotherapy should receive prophylactic therapy with nucleoside analogs, such as lamivudine to prevent HBV reactivation.[43,44]

3.5.2. Additional pretreatment tests (Table 1) may be performed in clinical trials or in the presence of specific clinical problems.

3.5.2.1. The assessment of molecular cytogenetics (FISH) before therapy is recommended.

3.5.2.2. CT scans generally are not required for the initial evaluation or follow-up. Moreover, the staging of CLL does not use CT scans but relies on physical examination and blood counts. Results of a recent study suggest that the presence of abdominal disease (splenomegaly or lymphadenopathy) as detected by CT scan in patients with Rai stage 0 predicts a more aggressive clinical course.[45] Therefore, clinical studies evaluating the use of CT scans in CLL are strongly encouraged. Moreover, enlarged lymph nodes if detected only by CT scan do not change the clinical Binet or Rai stage.

In clinical trials, in which the treatment intent is to maximize complete remission (CR), chest, abdominal, and pelvic CT scans are recommended to evaluate the response to therapy. One CT scan should be performed before the start of therapy and another CT scan at the first restaging after therapy if previously abnormal.

3.5.2.3. Other imaging methods. Except in patients with Richter transformation, positron emission tomography scans do not provide information that is useful in the management of CLL. Similarly, nuclear magnetic resonance imaging and other imaging techniques are generally not useful in the management of CLL.

3.5.2.4. Abdominal ultrasound. In some countries, the use of abdominal ultrasound is popular to assess the extent of lymphadenopathy and organomegaly in CLL. Although it may be used in the clinical management of individual patients, this methodology is strongly investigator-dependent and therefore should not be used for the response evaluation in clinical trials.

3.5.2.5. Lymph node biopsy. A lymph node biopsy is generally not required, unless such tissue is necessary for companion scientific studies or in rare cases with difficult diagnosis. A lymph node biopsy is required to establish the diagnosis of a transformation into an aggressive lymphoma (Richter syndrome).

Table 2. Recommendations regarding indications for treatment in CLL

	General practice	Clinical trial
Treat with Rai stage 0	NGI*	RQ
Treat with Binet stage A	NGI*	RQ
Treat with Binet stage B or Rai stage I or Rai stage II	Possible*	Possible*
Treat with Binet stage C or Rai stage III or Rai stage IV	Yes	Yes
Treatment of active/progressive disease	Yes	Yes
Treat without active/progressive disease	NGI	RQ

General practice is defined as the use of accepted treatment options for a patient with CLL who is not enrolled in a clinical trial.

NGI indicates not generally indicated; and RQ, research question.

*Treatment is indicated if the disease is active as defined in section 4.

Table 3. Recommendations regarding the response assessment in CLL patients

Diagnostic test	Section of guidelines	General practice	Clinical trial
History, physical examination	5.1.2, 5.1.3, 5.1.4, 5.2.2, 5.2.3, 5.3.1, 5.3.2	Always	Always
CBC and differential count	5.1.1, 5.1.5, 5.2.4, 5.3.3, 5.3.5	Always	Always
Marrow aspirate and biopsy	5.1.6	At cytopenia of uncertain cause	At CR or cytopenia of uncertain cause
Assessment for minimal residual disease	5.9	NGI	Desirable
Ultrasound of the abdomen*	5.1.2, 5.1.3, 5.2.2, 5.2.3, 5.3.1, 5.3.2	Possible, if previously abnormal	NGI
CT scans of chest, pelvis, and abdomen	5.1.2, 5.1.3, 5.2.2, 5.2.3, 5.3.1, 5.3.2	NGI	Recommended if previously abnormal and otherwise with a CR

General practice is defined as the use of accepted treatment options for a patient with CLL who is not enrolled in a clinical trial.
NGI indicates not generally indicated.
*Used in some countries to monitor lymphadenopathy and organomegaly.

4. Indications for treatment

4.1. Primary treatment decisions

Criteria for initiating treatment may vary depending on whether or not the patient is treated in a clinical trial (Table 2). In general practice, newly diagnosed patients with asymptomatic early-stage disease (Rai 0, Binet A) should be monitored without therapy unless they have evidence of disease progression. Studies from the French Cooperative Group on CLL,[46] the Cancer and Leukemia Group B,[47] the Spanish Group PETHEMA,[48] and the Medical Research Council[48] in the United Kingdom in patients with early-stage disease confirm that the use of alkylating agents in patients with early-stage disease does not prolong survival. This result was confirmed by a meta-analysis.[49] In one study, treated patients with early-stage disease had an increased frequency of fatal epithelial cancers compared with untreated patients.[46] Therefore, the potential benefit, if any, of an early intervention therapy with antileukemia drugs, alone or in combination with monoclonal antibodies, requires further study.

Whereas patients at intermediate (stages I and II) and high risk (stages III and IV) according to the modified Rai classification or at Binet stage B or C usually benefit from the initiation of treatment, some of these patients (in particular Rai intermediate risk or Binet stage B) can be monitored without therapy until they have evidence for progressive or symptomatic disease.

Active disease should be clearly documented for protocol therapy. At least one of the following criteria should be met:

1. Evidence of progressive marrow failure as manifested by the development of, or worsening of, anemia and/or thrombocytopenia

2. Massive (ie, at least 6 cm below the left costal margin) or progressive or symptomatic splenomegaly

3. Massive nodes (ie, at least 10 cm in longest diameter) or progressive or symptomatic lymphadenopathy

4. Progressive lymphocytosis with an increase of more than 50% over a 2-month period or lymphocyte doubling time (LDT) of less than 6 months. LDT can be obtained by linear regression extrapolation of absolute lymphocyte counts obtained at intervals of 2 weeks over an observation period of 2 to 3 months. In patients with initial blood lymphocyte counts of less than 30×10^9/L (30 000/μL), LDT should not be used as a single parameter to define a treatment indication. In addition, factors contributing to lymphocytosis or lymphadenopathy other than CLL (eg, infections) should be excluded.

5. Autoimmune anemia and/or thrombocytopenia that is poorly responsive to corticosteroids or other standard therapy (see section 10.2).

6. Constitutional symptoms, defined as any one or more of the following disease-related symptoms or signs:

a. Unintentional weight loss of 10% or more within the previous 6 months;

b. significant fatigue (ie, ECOG PS 2 or worse; inability to work or perform usual activities);

c. fevers higher than 100.5°F or 38.0°C for 2 or more weeks without other evidence of infection; or

d. night sweats for more than 1 month without evidence of infection.

Hypogammaglobulinemia or monoclonal or oligoclonal paraproteinemia does not by itself constitute a basis for initiating therapy. However, it is recommended to assess the change of these protein abnormalities if patients are treated.

Patients with CLL may present with a markedly elevated leukocyte count; however, the symptoms associated with 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.

4.2. Second-line treatment decisions

In general, second-line treatment decisions follow the same indications as those used for initiation of first-line treatment. Patients who have resistant disease, a short time to progression after the first treatment, and/or leukemia cells with del(17p) often do not respond to standard chemotherapy and have a relatively short survival. Therefore, such patients should be offered investigative clinical protocols, including allogeneic hematopoietic stem cell transplantation.[50-54]

5. Definition of response, relapse, and refractory disease

Assessment of response should include a careful physical examination and evaluation of the blood and marrow (Tables 3,4).

5.1. Complete remission (CR)

CR requires all of the following criteria as assessed at least 2 months after completion of therapy:

5.1.1. Peripheral blood lymphocytes (evaluated by blood and differential count) below 4×10^9/L (4000/μL). In clinical trials, the presence of minimal residual disease (MRD) after therapy should be assessed (see section 5.9). The sensitivity of the method used to evaluate for MRD should be reported.

Table 4. Response definition after treatment for patients with CLL, using the parameters of Tables 1 and 3

Parameter	CR*	PR*	PD*
Group A			
Lymphadenopathy†	None > 1.5 cm	Decrease ≥ 50%	Increase ≥ 50%
Hepatomegaly	None	Decrease ≥ 50%	Increase ≥ 50%
Splenomegaly	None	Decrease ≥ 50%	Increase ≥ 50%
Blood lymphocytes	< 4000/μL	Decrease ≥ 50% from baseline	Increase ≥ 50% over baseline
Marrow‡	Normocellular, < 30% lymphocytes, no B-lymphoid nodules. Hypocellular marrow defines CRi (5.1.6).	50% reduction in marrow infiltrate, or B-lymphoid nodules	
Group B			
Platelet count	> 100 000/μL	> 100 000/μL or increase ≥ 50% over baseline	Decrease of ≥ 50% from baseline secondary to CLL
Hemoglobin	> 11.0 g/dL	> 11 g/dL or increase ≥ 50% over baseline	Decrease of > 2 g/dL from baseline secondary to CLL
Neutrophils‡	> 1500/μL	> 1500/μL or > 50% improvement over baseline	

Group A criteria define the tumor load, group B criteria define the function of the hematopoietic system (or marrow).

*CR (complete remission): all of the criteria have to be met, and patients have to lack disease-related constitutional symptoms; PR (partial remission): at least two of the criteria of group A plus one of the criteria of group B have to be met; SD is absence of progressive disease (PD) and failure to achieve at least a PR; PD: at least one of the above criteria of group A or group B has to be met.

†Sum of the products of multiple lymph nodes (as evaluated by CT scans in clinical trials, or by physical examination in general practice).

‡These parameters are irrelevant for some response categories.

5.1.2. Absence of significant lymphadenopathy (eg, lymph nodes >1.5 cm in diameter) by physical examination. In clinical trials, a CT scan of the abdomen, pelvis, and thorax is desirable if previously abnormal. Lymph nodes should not be larger than 1.5 cm in diameter.

5.1.3. No hepatomegaly or splenomegaly by physical examination. In clinical trials, a CT scan of the abdomen should be performed at response assessment if found to be abnormal before therapy or if physical examination is inconclusive at the time of evaluation.

5.1.4. Absence of constitutional symptoms.

5.1.5. Blood counts above the following values:

5.1.5.1. Neutrophils more than 1.5 × 10^9/L (1500/μL) without need for exogenous growth factors.

5.1.5.2. Platelets more than 100 × 10^9/L (100 000/μL) without need for exogenous growth factors.

5.1.5.3. Hemoglobin more than 110 g/L (11.0 g/dL) without red blood cell transfusion or need for exogenous erythropoietin.

5.1.6. For patients in clinical trials (Table 3), a marrow aspirate and biopsy should be performed at least 2 months after the last treatment and if clinical and laboratory results listed in sections 5.1.1 through 5.1.5 demonstrate that a CR has been achieved. To define a CR, the marrow sample must be at least normocellular for age, with less than 30% of nucleated cells being lymphocytes. Lymphoid nodules should be absent.

In some cases, lymphoid nodules can be found, which often reflect residual disease.[55,56] These nodules should be recorded as "nodular PR." Moreover, immunohistochemistry should be performed to define whether these nodules are composed primarily of T cells or lymphocytes other than CLL cells or of CLL cells. If the marrow is hypocellular, a repeat determination should be performed after 4 weeks, or until peripheral blood counts have recovered. However, this time interval should not exceed 6 months after the last treatment. A marrow biopsy should be compared with that of pretreatment marrow. In general practice, the use of a marrow biopsy for evaluating a CR is at the discretion of the physician.

In clinical trials aiming at maximizing the CR rate, the quality of the CR should be assessed for MRD by flow cytometry (see section 5.9) or by immunohistochemistry (IHC).

5.1.7. A controversial issue is how best to categorize the response of patients who fulfill all the criteria for a CR (including the marrow examinations described in section 5.16) but who have a persistent anemia or thrombocytopenia or neutropenia apparently unrelated to CLL but related to drug toxicity. We recommend that these patients be considered as a different category of remission: CR with incomplete marrow recovery (CRi). For the definition of this category, CRi, the marrow evaluation (see section 5.1.6) should be performed with scrutiny and not show any clonal infiltrate. In clinical trials, CRi patients should be monitored prospectively to determine whether their outcome differs from that of patients with detectable residual disease or with noncytopenic CR.

5.2. Partial remission (PR)

PR is defined by the criteria described in sections 5.2.1, 5.2.2, or 5.2.3 (if abnormal before therapy), as well as one or more of the features listed in section 5.2.4. To define a PR, these parameters need to be documented for a minimal duration of 2 months (Table 4). Constitutional symptoms persisting for more than 1 month should be recorded.

5.2.1. A decrease in the number of blood lymphocytes by 50% or more from the value before therapy.

5.2.2. Reduction in lymphadenopathy (by CT scans in clinical trials[57] or by palpation in general practice) as defined by the following:

5.2.2.1. A decrease in lymph node size by 50% or more either in the sum products of up to 6 lymph nodes, or in the largest diameter of the enlarged lymph node(s) detected prior to therapy.

5.2.2.2. No increase in any lymph node, and no new enlarged lymph node. In small lymph nodes (< 2 cm), an increase of less than 25% is not considered to be significant.

5.2.3. A reduction in the noted pretreatment enlargement of the spleen or liver by 50% or more, as detected by CT scan (in clinical trials) or palpation (in general practice).

5.2.4. The blood count should show one of the following results:

5.2.4.1. Neutrophils more than 1.5 × 10^9/L (1500/μL) without need for exogenous growth factors.

Table 5. Grading scale for hematologic toxicity in CLL studies

Grade*	Decrease in platelets† or Hb‡ (nadir) from pretreatment value, %	Absolute neutrophil count/μL§ (nadir)
0	No change to 10%	≥ 2000
1	11%-24%	≥ 1500 and < 2000
2	25%-49%	≥ 1000 and < 1500
3	50%-74%	≥ 500 and < 1000
4	≥ 75%	< 500

*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 5.

†Platelet counts must be below normal levels for grades 1 to 4. If, at any level of decrease, the platelet count is $< 20 \times 10^9$/L (20 000/μL), this will be considered grade 4 toxicity, unless a severe or life-threatening decrease in the initial platelet count (eg, 20×10^9/L [20 000/μL]) was present pretreatment, in which case the patient is not evaluable for toxicity referable to platelet counts.

‡Hb levels must be below normal levels for grades 1 to 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 absolute neutrophil count (ANC) reaches $< 1 \times 10^9$/L (1000/μL), it should be judged to be grade 3 toxicity. Other decreases in the white blood cell count, or in circulating neutrophils, 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 $< 1 \times 10^9$/L (1000/μL) before therapy, the patient is not evaluable for toxicity referable to the ANC. The use of growth factors such as G-CSF is not relevant to the grading of toxicity, but should be documented.

5.2.4.2. Platelet counts greater than 100×10^9/L (100 000/μL) or 50% improvement over baseline without need for exogenous growth factors.

5.2.4.3. Hemoglobin greater than 110 g/L (11.0 g/dL) or 50% improvement over baseline without requiring red blood cell transfusions or exogenous erythropoietin.

5.3. Progressive disease

Progressive disease during or after therapy is characterized by at least one of the following:

5.3.1. Lymphadenopathy. Progression of lymphadenopathy is often discovered by physical examination and should be recorded. In CLL, the use of CT scans usually does not add much information for the detection of progression or relapse.[58] Therefore, the use of imaging methods to follow CLL progression is at the discretion of the treating physician. Disease progression occurs if one of the following events is observed:

Appearance of any new lesion, such as enlarged lymph nodes (>1.5 cm), splenomegaly, hepatomegaly, or other organ infiltrates.

An increase by 50% or more in greatest determined diameter of any previous site.

5.3.2. An increase in the previously noted enlargement of the liver or spleen by 50% or more or the de novo appearance of hepatomegaly or splenomegaly.

5.3.3. An increase in the number of blood lymphocytes by 50% or more with at least 5000 B lymphocytes per microliter.

5.3.4. Transformation to a more aggressive histology (eg, Richter syndrome). Whenever possible, this diagnosis should be established by lymph node biopsy.

5.3.5. Occurrence of cytopenia (neutropenia, anemia, or thrombocytopenia) attributable to CLL.

5.3.5.1. During therapy. Cytopenias may occur as a side effect of many therapies and should be assessed according to Table 5. During therapy, cytopenias cannot be used to define disease progression. Each protocol should define the amount of drug(s) to be administered with such cytopenias.

5.3.5.2. After treatment. The progression of any cytopenia (unrelated to autoimmune cytopenia), as documented by a decrease of Hb levels by more than 20 g/L (2 g/dL) or to less than 100 g/L (10 g/dL), or by a decrease of platelet counts by more than 50% or to less than 100×10^9/L (100 000/μL), which occurs at least 3 months after treatment, defines disease progression, if the marrow biopsy demonstrates an infiltrate of clonal CLL cells.

5.4. Stable disease

Patients who have not achieved a CR or a PR, and who have not exhibited progressive disease, will be considered to have stable disease (which is equivalent to a nonresponse).

5.5. Treatment failure

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

5.6. Time to progression, progression-free survival, and overall survival

Time to progression (TTP) is defined as the time from study entry until objective disease progression (see section 5.3). Progression-free survival (PFS) is defined as the time from study entry until objective disease progression or death. Overall survival is defined as the time from study entry until death from any cause, and is measured in the intent-to-treat population.

5.7. Relapse

Relapse is defined as a patient who has previously achieved the above criteria (sections 5.1 and 5.2) of a CR or PR, but after a period of 6 or more months, demonstrates evidence of disease progression (see section 5.3).

5.8. Refractory disease

Refractory disease is defined as treatment failure (as defined in section 5.5) or disease progression within 6 months to the last antileukemic therapy. For the definition of "high-risk CLL" justifying the use of allogeneic stem cell transplantation,[59] the disease should be refractory to a purine analog-based therapy or to autologous hematopoietic stem cell transplantation.

5.9. Minimal residual disease

The complete eradication of the leukemia is an obvious desired endpoint. New detection technologies, such as multicolor flow cytometry and real-time quantitative PCR, have determined that many patients who achieved a CR by the 1996 NCI-WG guidelines have detectable MRD. Although eradication of MRD may improve prognosis, prospective clinical trials are needed to define whether additional treatment intended solely to eradicate MRD provides a significant benefit to clinical outcome. The techniques for assessing MRD have undergone a critical evaluation and have become fairly standard.[60] Either 4-color flow cytometry (MRD flow) or allele-specific oligonucleotide PCR is reliably sensitive down to a level of approximately one CLL cell in 10 000 leukocytes. As such, patients will be defined as having a clinical remission in the absence of MRD when they have blood or marrow with less than one CLL cell per 10 000 leukocytes. The blood generally can be used for making this assessment except during the period within 3 months of completing therapy, particularly for patients treated with alemtuzumab, rituximab, and other antibodies targeting CLL. In such

cases, it is essential to assess the marrow for MRD. Therefore, future clinical trials that aim toward achieving long-lasting CRs should include at least one test to assess MRD because the lack of leukemia persistence using these sensitive tests seems to have a strong, positive prognostic impact.[61-63]

6. Factors requiring stratification at inclusion in a clinical phase 3 trial

6.1. Patients ideally should be stratified with regard to previous treatment versus no previous treatment, and as purine analog–sensitive versus purine analog–refractory in studies for which prior therapy is allowed.

6.2. If more than one clinical stage is allowed, patients ideally should be stratified for stage.

6.3. Patients ideally should be stratified based on whether or not they have leukemia cells with del(17p) or del(11q).

7. Assessment of toxicity

Evaluation of treatment-related toxicity requires careful consideration of both the manifestations of the underlying disease and the anticipated adverse reactions to the agents used in therapy. For this reason, some of the conventional criteria used for assessing toxicity are not applicable to clinical studies involving patients with hematologic malignancies in general, or CLL in particular. An example is hematologic toxicity; patients with advanced CLL generally have cytopenias that may be caused by the underlying CLL and/or prior therapy. A few guidelines are presented to help evaluate for treatment-induced toxicity in CLL.

7.1. Hematologic toxicity

Evaluation of hematologic toxicity in patients with CLL must take into consideration that many patients have low blood cell counts at the initiation of therapy. Therefore, the standard criteria used for solid tumors cannot be applied, as many CLL patients then would be considered to have grade 2 to 4 hematologic toxicity at the initiation of treatment. Furthermore, the absolute blood neutrophil counts rarely are used at the initiation of therapy to modify the treatment dose because these values typically are unreliable in CLL patients with lymphocytosis. However, the increasing use of more effective therapeutic agents, particularly those with neutropenia as a dose-limiting toxicity (eg, nucleoside analogs), can result in clinically significant myelosuppression. Therefore, the 1996 guidelines proposed a new dose-modification scheme for quantifying hematologic deterioration in patients with CLL, which included alterations in the dose of myelosuppressive agents based on the absolute neutrophil count. This dose modification scheme has proven very helpful in the context of several large prospective trials in CLL and should be retained (Table 5).

7.2. Infectious complications

Patients with CLL are at increased risk for infection because of compromised immune function, which might be related to the disease itself and/or to the consequences of therapy. Nevertheless, the rate(s) of infection after treatment can be used in assessing the relative immune-suppressive effects of a given therapy. The etiology of the infection should be reported and categorized as bacterial, viral, or fungal, and as 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).

Particular attention should be given to monitoring for symptoms or laboratory evidence of infection with CMV in patients treated with agents, such as alemtuzumab (alone or in combination) or with allogeneic stem cell transplantation. In contrast, the infection rate seems low in patients younger than 65 years treated with fludarabine-based first-line therapy, where no routine anti-infective prophylaxis is required.[64]

7.3. Tumor lysis syndrome

CLL patients rarely experience tumor lysis syndrome after therapy with a purine analog-based regimen.[65] However, this might not be the case after treatment with newer agents or novel treatment modalities. For this reason, patients in early-phase clinical trials should be monitored for possible tumor lysis syndrome, which should be treated appropriately. If observed, the occurrence and severity of tumor lysis syndrome should be recorded in clinical trials.

7.4. Nonhematologic toxicities

Other nonhematologic toxicities should be graded according to the latest version of the NCI Common Toxicity Criteria.[66]

8. Reporting of clinical response data

Clear and careful reporting of data are 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 and refractory disease are defined in sections 5.7 and 5.8. For those patients who have relapsed, it is also useful to describe the quality and duration of their prior response.

9. Treatment endpoints

Given the recent increase of treatment options for CLL patients, the choice of treatment and the end points of clinical trials may depend on the fitness of the patients (see section 3.1). For example, the number of MRD-negative CRs or the overall survival might be appropriate end points in physically fit patients. In contrast, trials on patients with reduced physical fitness might choose the time to progression or health-related quality of life as trial end points. Moreover, recent data suggest that the quality of life in CLL patients is reduced compared with the normal population and only moderately increased by some of the current treatment options.[67-70] Therefore, further studies assessing the health-related quality of life in CLL are strongly encouraged.

10. Supportive care and management of complications

10.1. Indications for growth factors in CLL

While under myelosuppressive (chemo-)therapy, growth factors, such as G-CSF, should be given according to the guidelines of the

American Society of Clinical Oncology.[71] The use of G-CSF also might benefit patients who experience prolonged cytopenias after treatment with alemtuzumab. Similarly, some CLL patients with anemia may benefit from erythropoiesis stimulating factors if used according to recently published guidelines.[72,73] However, it should be pointed out that CLL-related cytopenias are often efficiently corrected by an appropriate antileukemic therapy.

10.2. Autoimmune hemolytic anemia or autoimmune thrombocytopenia

Immune thrombocytopenic purpura (ITP) and autoimmune hemolytic anemia (AIHA) as a single abnormality caused by CLL initially should be treated with glucocorticoids and not chemotherapy. Second-line treatment options for AIHA include splenectomy, intravenous immunoglobulins, and/or immunosuppressive therapy with agents, such as cyclosporine A, azathioprine, or low-dose cyclophosphamide. Good responses also have been obtained with antibody therapy using agents as rituximab or alemtuzumab.[74-76] Treatment refractory autoimmune cytopenias can be an indication for chemotherapy or chemoimmunotherapy directed at the underlying CLL.[77] In this regard, the Binet or Rai staging systems do not distinguish between ITP/AIHA or marrow infiltration as the cause for anemia or thrombocytopenia that results in classifying a patient as having stage C or high-risk disease.

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