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Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma, Version 1.2015

Clinical Practice Guidelines in Oncology

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Overview

Chronic lymphocytic leukemia (CLL) remains the most prevalent adult leukemia in Western countries, but it is considered rare in regions such as East Asia.

Abstract

Chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL) are different manifestations of the same disease, which are managed in the same way. The advent of novel monoclonal antibodies (ofatumumab and obinutuzumab) led to the development of effective chemoimmunotherapy regimens. The recently approved small molecule kinase inhibitors (ibrutinib and idelalisib) are effective treatment options for CLL in elderly patients with decreased tolerance for aggressive regimens and in patients with poor prognostic features who do not benefit from conventional chemoimmunotherapy regimens. This portion of the NCCN Guidelines for Non-Hodgkin's Lymphomas describes the recent specific to the incorporation of recently approved targeted therapies for the management of patients with newly diagnosed and relapsed or refractory CLL/SLL. (J Natl Compr Canc Netw 2015;13:326–362)

NCCN Categories of Evidence and Consensus

Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.

Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise noted.

Clinical trials: NCCN believes that the best management for any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

Please Note

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) are a statement of consensus of the authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult the NCCN Guidelines® is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment. The National Comprehensive Cancer Network® (NCCN®) makes no representation or warranties of any kind regarding their content, use, or application and disclaims any responsibility for their applications or use in any way. The full NCCN Guidelines for Non-Hodgkin's Lymphomas are not printed in this issue of JNCCN but can be accessed online at NCCN.org.

Disclosures for the NCCN Non-Hodgkin's Lymphomas Panel

At the beginning of each NCCN Guidelines panel meeting, panel members review all potential conflicts of interest. NCCN, in keeping with its commitment to public transparency, publishes these disclosures for panel members, staff, and NCCN itself.

Individual disclosures for the NCCN Non-Hodgkin's Lymphomas Panel members can be found on page 362. (The most recent version of these guidelines and accompanying disclosures are available on the NCCN Web site at NCCN.org.)

These guidelines are also available on the Internet. For the latest update, visit NCCN.org.

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Chronic Lymphocytic Leukemia/
Small Lymphocytic Lymphoma

CLL/small lymphocytic lymphoma (SLL) constitutes approximately 7% of newly diagnosed cases of non-Hodgkin's lymphoma (NHL).[1] In 2015, an estimated 14,620 people will be diagnosed with CLL in the United States, and an estimated 4650 people will die of the disease.[2] Morphologically, the leukemic cells appear as small, mature lymphocytes that may be found admixed with occasional larger or atypical cells, or prolymphocytes.[3] CLL and SLL are different manifestations of the same disease and are managed in much the same way.[4] CLL/SLL is characterized by progressive accumulation of these leukemic cells in the peripheral blood, bone marrow, and lymphoid tissues. The major difference is that in CLL, a significant number of the abnormal lymphocytes are also found in the bone marrow and blood, while in SLL the abnormal lymphocytes are predominantly found in the lymph nodes and bone marrow.

Diagnosis

The diagnosis of CLL requires the presence of at least 5000 clonal B cells/mcL (5 x 10^9/L) in the peripheral blood, which is established by flow cytometry quantification.[3] The presence of fewer B cells in the absence of palpable lymphadenopathy or other clinical features characteristic of a lymphoproliferative disorder is defined as monoclonal B lymphocytosis (MBL). MBL is a relatively recent diagnostic category describing individuals who present with an abnormal B-cell population with the immunophenotype of CLL but do not meet the diagnostic crite-

DIAGNOSIS[a]

ESSENTIAL:
- Hematopathology review of all slides with at least one paraffin block representative of the tumor, if the diagnosis was made on a lymph node or bone marrow biopsy. Rebiopsy if consult material is nondiagnostic.
- Flow cytometry of blood adequate for diagnosis of CLL/SLL (biopsy generally not required)
  - ➤ CLL diagnosis requires presence of monoclonal B lymphocytes $\geq 5 \times 10^9$/L in peripheral blood
  - ➤ Clonality of B cells should be confirmed by flow cytometry
  - ➤ Adequate immunophenotyping to establish diagnosis by flow cytometry using cell surface markers:[b,c] kappa/lambda, CD19, CD20, CD5, CD23, CD10; if flow is used to establish diagnosis, also include cytospin for cyclin D1 or FISH for t(11;14); t(11q;v)
  - ➤ SLL diagnosis requires presence of lymphadenopathy and/or splenomegaly with B lymphocytes $\leq 5 \times 10^9$/L in peripheral blood
  - ➤ SLL diagnosis should be confirmed by histopathology evaluation of lymph node biopsy
- If diagnosis is not established by flow cytometry, then proceed with lymph node biopsy. An FNA or core needle biopsy alone is not generally suitable for the initial diagnosis of lymphoma. In certain circumstances, when a lymph node is not easily accessible for excisional or incisional biopsy, a combination of core biopsy and FNA biopsies in conjunction with appropriate ancillary techniques for the differential diagnosis (immunohistochemistry, flow cytometry) may be sufficient for diagnosis.
  - ➤ Adequate immunophenotyping to establish diagnosis by IHC panel:[b,c] CD3, CD5, CD10, CD20, CD23, cyclin D1
- Absolute monoclonal B lymphocyte count[d]

INFORMATIVE FOR PROGNOSTIC AND/OR THERAPY DETERMINATION:[e]
- FISH to detect: +12; del(11q); del(13q); del(17p); or stimulated cytogenetics to detect: +12; del(11q); del(13q); del(17p) or complex karyotype
- Molecular analysis to detect: IGHV mutation status
- Determination of CD38 and ZAP-70 expression by flow cytometry, methylation, or immunohistochemistry[f]
- TP53 sequencing

CLL/SLL → See Workup for CLL/SLL (CSLL-2)

Monoclonal B-cell lymphocytosis (MBL)
- Absolute monoclonal B lymphocyte count <5000/mm³
- All lymph nodes <1.5 cm
- No anemia
- No thrombocytopenia

→ Observe

*Available online, in these guidelines, at NCCN.org.

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[a] CLL = chronic lymphocytic leukemia; SLL = small lymphocytic lymphoma. Cases diagnosed as B-PLL are excluded from this guideline.

[b] Typical immunophenotype: CD5+, CD23+, CD43+/-, CD10-, CD19+, CD20 dim, sIg dim+, and cyclin D1-. Note: Some cases may be sIg bright+, CD23- or dim, and some MCL may be CD23+; cyclin D1 immunohistochemistry or FISH for t(11;14) should be considered in all cases and should be done in cases with an atypical immunophenotype (CD23 dim or negative, CD20 bright, sIg bright).

[c] See Use of Immunophenotyping/Genetic Testing in Differential Diagnosis of Mature B-Cell and NK/T-Cell Neoplasms (NHODG-A*).

[d] Absolute monoclonal B lymphocyte count <5000/mm³ in the absence of adenopathy or other clinical features of lymphoproliferative disorder is MBL. Cells of same phenotype may be seen in reactive lymph nodes; therefore, diagnosis of SLL should only be made when effacement of lymph node architecture is seen.

[e] See Prognostic Information for CLL (CSLL-A).

[f] Evaluation of ZAP-70 expression can be challenging and ZAP-70 is not recommended outside the setting of a clinical trial. Methylation status is not widely available outside of a clinical trial.

CSLL-1

Clinical trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged. All recommendations are category 2A unless otherwise indicated.

Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma, Version 1.2015

WORKUP

ESSENTIAL:
- Physical exam: attention to node-bearing areas, including Waldeyer's ring, and to size of liver and spleen
- Performance status
- B symptoms
- CBC, differential, platelets
- Comprehensive metabolic panel
- Hepatitis B testing[g] if CD20 monoclonal antibody contemplated
- MUGA scan/echocardiogram if anthracycline- or anthracenedione-based regimen is indicated
- Pregnancy testing in women of child-bearing age (if chemotherapy planned)

USEFUL UNDER CERTAIN CIRCUMSTANCES:
- Quantitative immunoglobulins
- Reticulocyte count, haptoglobin, and direct Coombs' test
- Chest/abdominal/pelvic CT should be done prior to initiation of therapy (particularly when peripheral adenopathy is present and symptoms suggest bulky lymph nodes)
- Beta-2-microglobulin
- LDH
- Uric acid
- Unilateral bone marrow biopsy (± aspirate) at initiation of therapy
- Discussion of fertility issues and sperm banking
- PET scan is generally not useful in CLL but can assist in directing nodal biopsy if Richter's transformation is suspected

SLL/Localized
(Ann Arbor Stage I)
(See CSLL-3)

CLL (Rai Stages 0–IV) or SLL
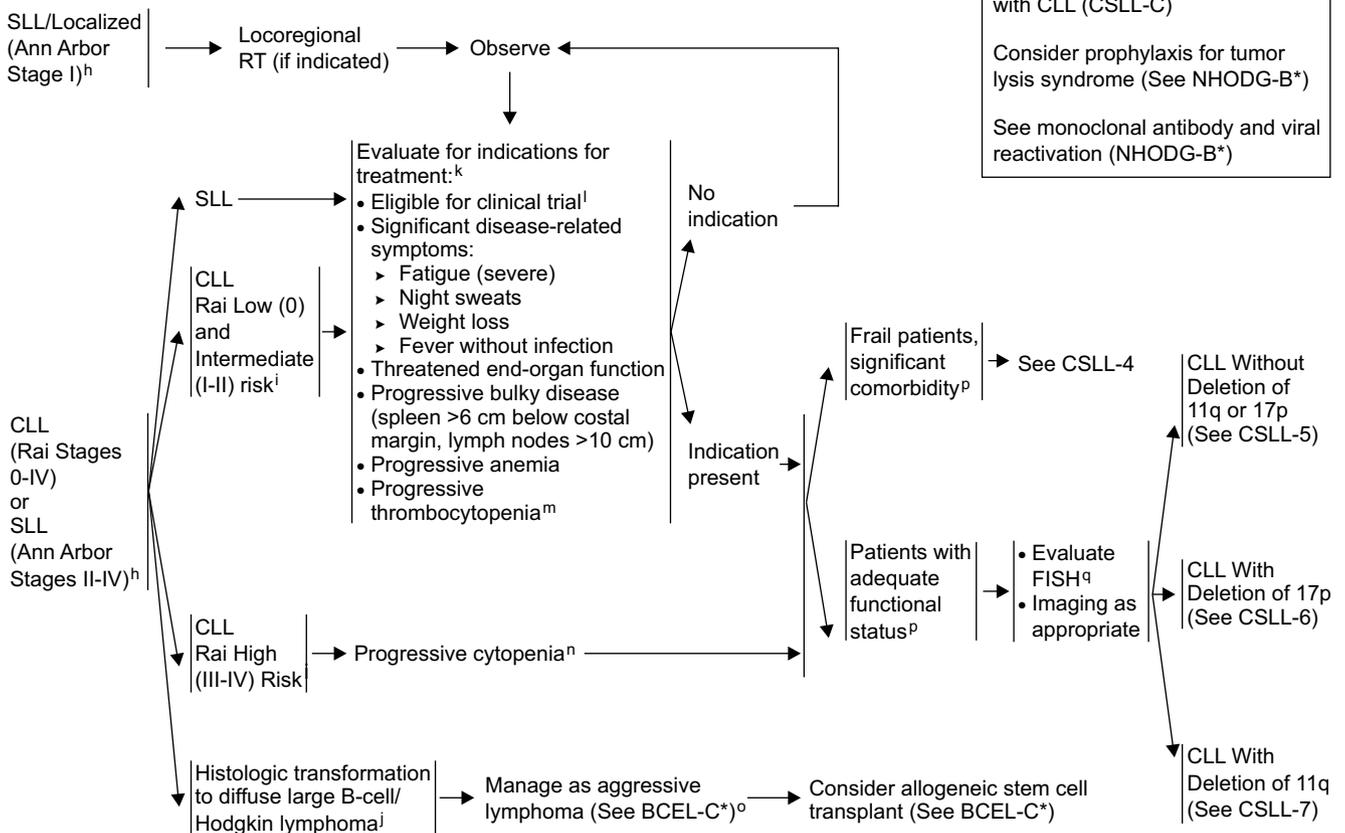(Ann Arbor Stage II–IV)
(See CSLL-3)

[g]Hepatitis B testing is indicated because of the risk of reactivation with immunotherapy + chemotherapy. Tests include hepatitis B surface antigen and core antibody for a patient with no risk factors. For patients with risk factors or previous history of hepatitis B, add e-antigen. If positive, check viral load and consult with gastroenterologist.

CSLL-2

PRESENTATION

See Supportive Care for Patients with CLL (CSLL-C)

Consider prophylaxis for tumor lysis syndrome (See NHODG-B*)

See monoclonal antibody and viral reactivation (NHODG-B*)

SLL/Localized (Ann Arbor Stage I)[h] → Locoregional RT (if indicated) → Observe

CLL (Rai Stages 0-IV) or SLL (Ann Arbor Stages II-IV)[h]

SLL

CLL Rai Low (0) and Intermediate (I-II) risk[i]

Evaluate for indications for treatment:[k]
• Eligible for clinical trial[l]
• Significant disease-related symptoms:
  ‣ Fatigue (severe)
  ‣ Night sweats
  ‣ Weight loss
  ‣ Fever without infection
• Threatened end-organ function
• Progressive bulky disease (spleen >6 cm below costal margin, lymph nodes >10 cm)
• Progressive anemia
• Progressive thrombocytopenia[m]

No indication → Observe

Indication present

Frail patients, significant comorbidity[p] → See CSLL-4

Patients with adequate functional status[p] → • Evaluate FISH[q] • Imaging as appropriate

CLL Without Deletion of 11q or 17p (See CSLL-5)

CLL With Deletion of 17p (See CSLL-6)

CLL With Deletion of 11q (See CSLL-7)

CLL Rai High (III-IV) Risk → Progressive cytopenia[n]

Histologic transformation to diffuse large B-cell/Hodgkin lymphoma[j] → Manage as aggressive lymphoma (See BCEL-C*)[o] → Consider allogeneic stem cell transplant (See BCEL-C*)

*Available online, in these guidelines, at NCCN.org.

[h] See Supportive Care for Patients with CLL (CSLL-C).
[i] See Rai and Binet Classification Systems (CSLL-B).
[j] Increased prolymphocytes in blood (>5%–<55%) (so-called "CLL-PL" or CLL with increased prolymphocytes) as well as the presence of expanded proliferation centers (broader than a 20x field) or a high proliferation rate (either >2.4 mitoses/proliferation center or Ki-67 >40%/proliferation center) on lymph node biopsy (so-called "accelerated CLL") are associated with more aggressive disease and poorer outcome; neither of these findings is considered to represent Richter's transformation and optimal management has not been established.
[k] Absolute lymphocyte count alone is not an indication for treatment unless above 200–300 x 10⁹/L or symptoms related to leukostasis.

[l] Given incurability with conventional therapy, consider a clinical trial as first line of treatment.
[m] Platelet counts >100,000 cells/mm³ are typically not associated with clinical risk.
[n] Select patients with mild, stable cytopenia (ANC<1000/μL, Hgb <11 g/dL, or platelet <100,000/μL) may continue to be followed with observation.
[o] In addition to the regimens listed in BCEL-C*, R-HyperCVAD has also been used in this setting.
[p] Salvi F, Miller MD, Grilli A, et al. A manual of guidelines to score the modified cumulative illness rating scale and its validation in acute hospitalized elderly patients. J Am Geriatr Soc 2008;56:1926-1931.
[q] Re-evaluation of FISH [t(11;14); t(11q;v); +12; del(11q); del(13q); del(17p)] is necessary to direct treatment.

CSLL-3

Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma, Version 1.2015

FRAIL PATIENTS, SIGNIFICANT COMORBIDITY

FIRST-LINE
THERAPY

RELAPSED/
REFRACTORY
THERAPY

See Supportive Care for Patients
with CLL (CSLL-C)

Consider prophylaxis for tumor
lysis syndrome (See NHODG-B)

See monoclonal antibody and
viral reactivation (NHODG-B*)

Frail patients, significant
comorbidity[p] (not able to
tolerate purine
analogs)[h,k,l] ⟶ See Suggested Regimens
(CSLL-D 1 of 7) ⟶ See Suggested Regimens
(CSLL-D 2 of 7)

*Available online, in these guidelines, at NCCN.org.

[h] See Supportive Care for Patients with CLL (CSLL-C).
[k] Absolute lymphocyte count alone is not an indication for treatment unless above 200–300 x 10^9/L or symptoms related to leukostasis.
[l] Given incurability with conventional therapy, consider a clinical trial as first line of treatment.
[p] Salvi F, Miller MD, Grilli A, et al. A manual of guidelines to score the modified cumulative illness rating scale and its validation in acute hospitalized elderly patients. J Am Geriatr Soc 2008;56:1926-1931.

CSLL-4

CLL WITHOUT DELETION OF 11q or 17p
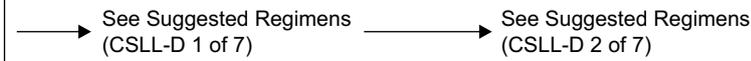
FIRST-LINE THERAPY

RELAPSED/ REFRACTORY THERAPY

See Supportive Care for Patients with CLL (CSLL-C)

Consider prophylaxis for tumor lysis syndrome (See NHODG-B*)

See monoclonal antibody and viral reactivation (NHODG-B*)

CLL without del (11q) or del (17p)[h,k,l]

→ Age ≥70 y and younger patients with significant comorbidities[p] → See Suggested Regimens (CSLL-D 1 of 7) → Relapsed CLL with indication for treatment (See CSLL-3) →
- Reevaluate FISH
- See Suggested Relapsed/ Refractory Therapy Regimens for age ≥70 y and younger patients with comorbidities
  ➤ CLL without del(11q) or del(17p), see CSLL-D 2 of 7

→ Age <70 y without significant comorbidities[p] → See Suggested Regimens (CSLL-D 1 of 7) → Relapsed CLL with indication for treatment (See CSLL-3) →
- Reevaluate FISH
- See Suggested Relapsed/ Refractory Therapy Regimens for age <70 y without significant comorbidities
  ➤ CLL without del(11q) or del(17p), see CSLL-D 2 of 7

→ Consider allogeneic stem cell transplant, if without significant comorbidities[p]

*Available online, in these guidelines, at NCCN.org.

[h] See Supportive Care for Patients with CLL (CSLL-C).
[k] Absolute lymphocyte count alone is not an indication for treatment unless above 200–300 x 10^9/L or symptoms related to leukostasis.
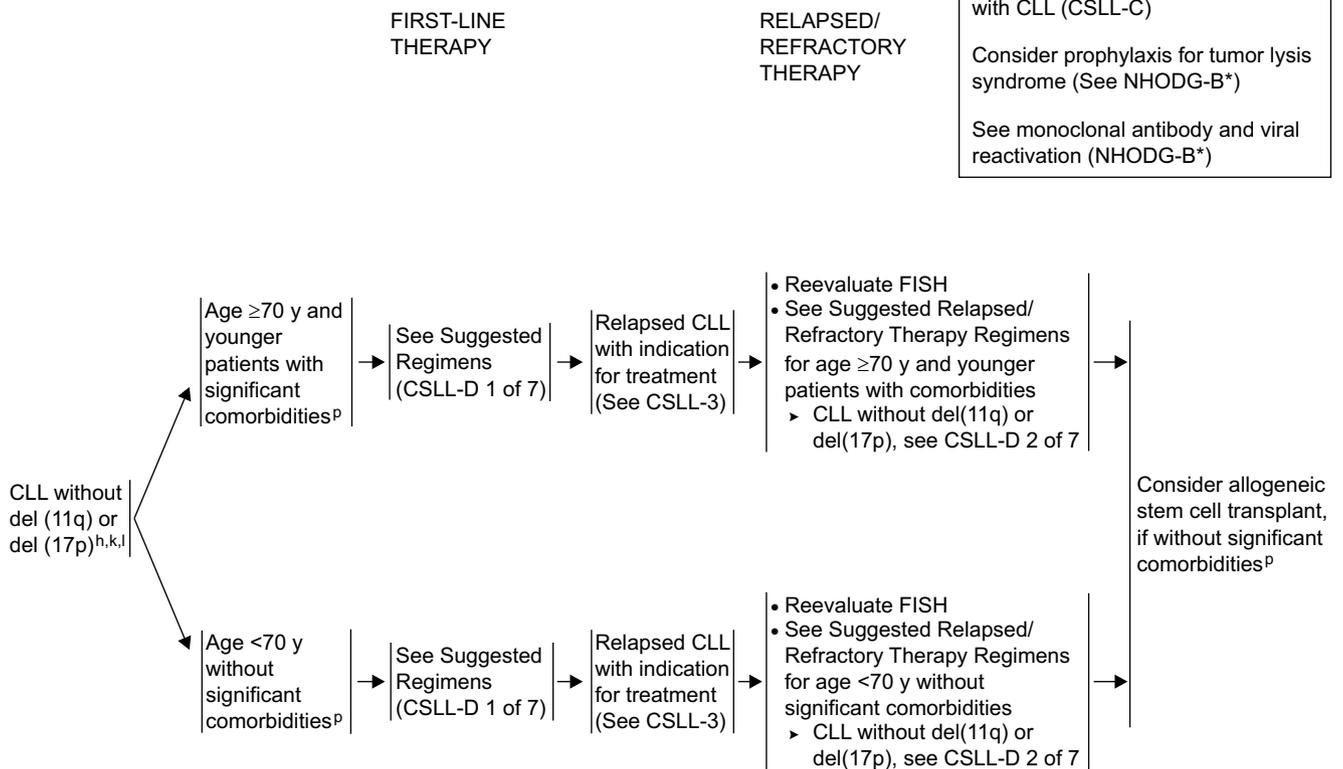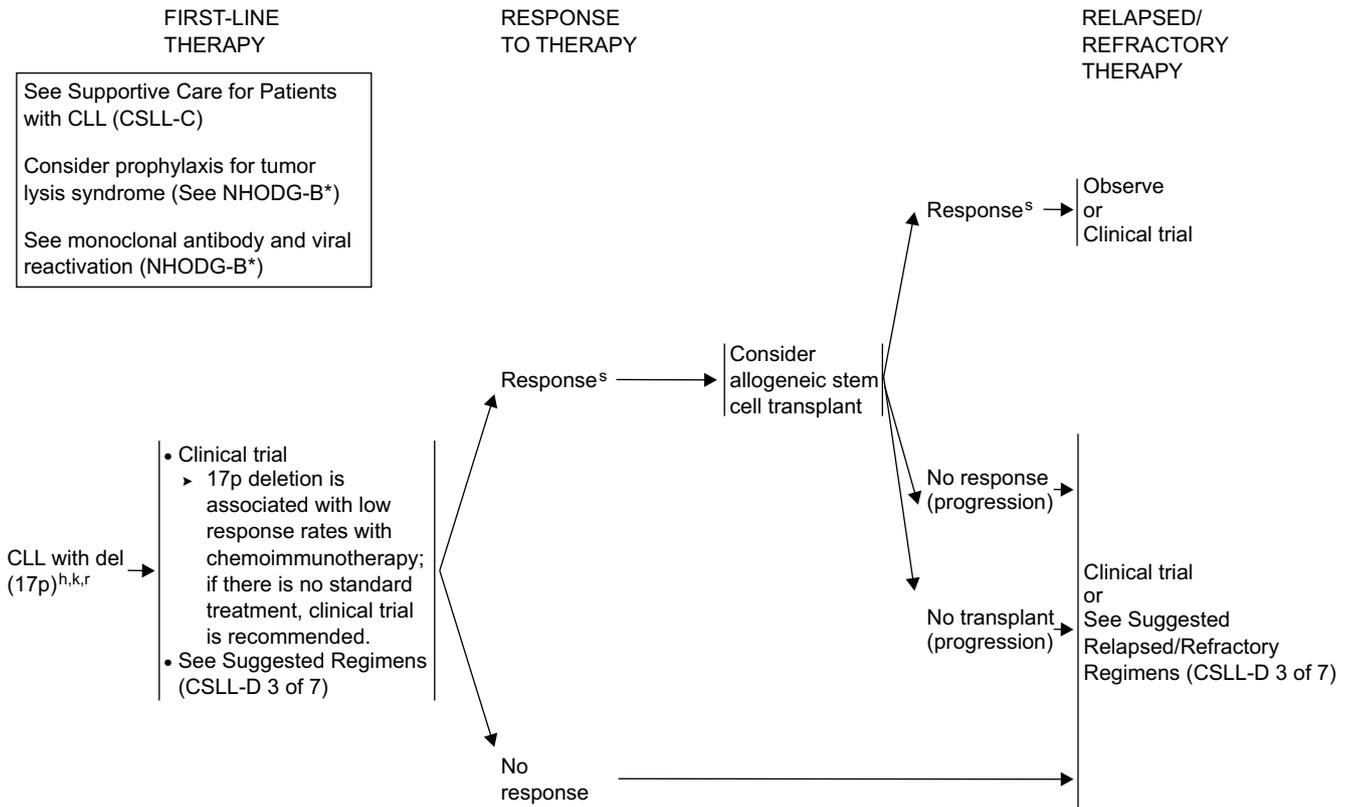[l] Given incurability with conventional therapy, consider a clinical trial as first line of treatment.
[p] Salvi F, Miller MD, Grilli A, et al. A manual of guidelines to score the modified cumulative illness rating scale and its validation in acute hospitalized elderly patients. J Am Geriatr Soc 2008;56:1926-1931.

CSLL-5

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CLL WITH DELETION OF 17p

FIRST-LINE
THERAPY

RESPONSE
TO THERAPY

RELAPSED/
REFRACTORY
THERAPY

See Supportive Care for Patients
with CLL (CSLL-C)

Consider prophylaxis for tumor
lysis syndrome (See NHODG-B*)

See monoclonal antibody and viral
reactivation (NHODG-B*)

CLL with del
(17p)[h,k,r]

- Clinical trial
  - 17p deletion is
    associated with low
    response rates with
    chemoimmunotherapy;
    if there is no standard
    treatment, clinical trial
    is recommended.
- See Suggested Regimens
  (CSLL-D 3 of 7)

Response[s] → Consider allogeneic stem cell transplant

No response

Response[s] → Observe or Clinical trial

No response (progression)

No transplant (progression)

Clinical trial or See Suggested Relapsed/Refractory Regimens (CSLL-D 3 of 7)

*Available online, in these guidelines, at NCCN.org.

[h] See Supportive Care for Patients with CLL (CSLL-C).
[k] Absolute lymphocyte count alone is not an indication for treatment unless above 200–300 x 10^9/L or symptoms related to leukostasis.
[r] Patients with low positivity should be retested due to chance of false-positive results.
[s] See Response Criteria: CLL (CSLL-E) or SLL (NHODG-C*).

CSLL-6

CLL WITH DELETION OF 11q

FIRST-LINE THERAPY

RESPONSE TO THERAPY

See Supportive Care for Patients with CLL (CSLL-C)

Consider prophylaxis for tumor lysis syndrome (See NHODG-B*)

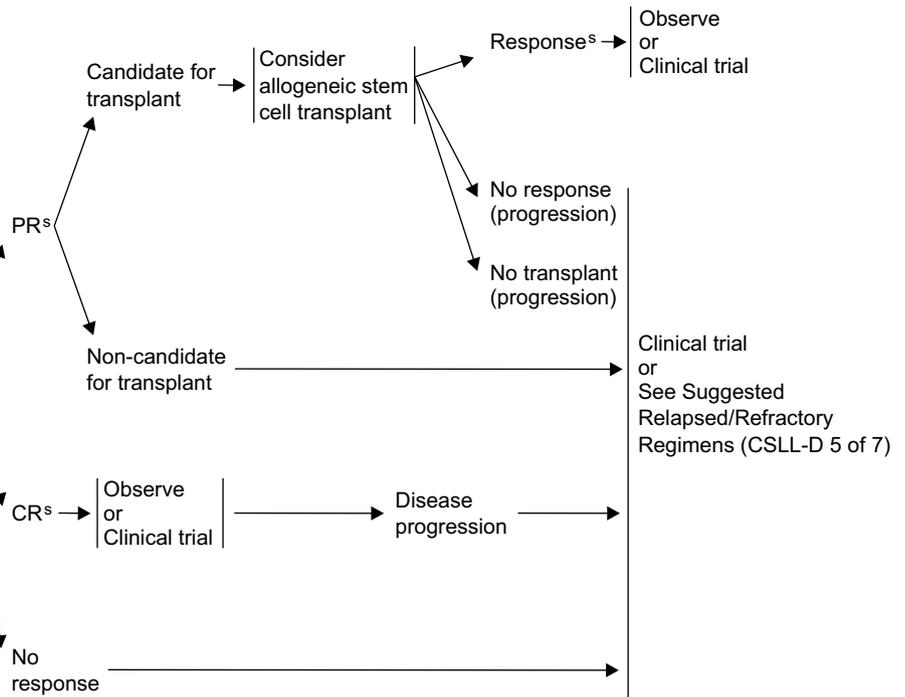See monoclonal antibody and viral reactivation (NHODG-B*)

RELAPSED/ REFRACTORY THERAPY

CLL with del (11q)[h,k]
• Outcomes are more favorable in patients who receive chemo-immunotherapy regimens containing an alkylating agent.

• Clinical trial
• See Suggested Regimens (CSLL-D 4 of 7)

PR[s]

Candidate for transplant → Consider allogeneic stem cell transplant

Response[s] → Observe or Clinical trial

No response (progression)

No transplant (progression)

Non-candidate for transplant

CR[s] → Observe or Clinical trial → Disease progression

No response

Clinical trial or See Suggested Relapsed/Refractory Regimens (CSLL-D 5 of 7)

*Available online, in these guidelines, at NCCN.org.

[h]See Supportive Care for Patients with CLL (CSLL-C).
[k]Absolute lymphocyte count alone is not an indication for treatment unless above 200–300 x 10^9/L or symptoms related to leukostasis.
[s]See Response Criteria: CLL (CSLL-E) or SLL (NHODG-C).

CSLL-7

Clinical trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged. All recommendations are category 2A unless otherwise indicated.

Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma, Version 1.2015

PROGNOSTIC INFORMATION FOR CLL[a]

Immunoglobulin Heavy-Chain Variable (IGHV) Region Gene Mutation and Surrogates by Flow Cytometry

	Outcome Association	
	Favorable	Unfavorable
DNA sequencing[b] IGHV	>2% mutation	≤2% mutation
Flow Cytometry CD38 Zap 70	<30% <20%	≥30% ≥20%

Interphase Cytogenetics (FISH)[c]

Unfavorable	Neutral	Favorable
del(11q) del(17p)	Normal +12	del(13q) (as a sole abnormality)

Complex karyotype[d]

Unfavorable
≥3 unrelated chromosome abnormalities in more than one cell on karyotype

[a]This table provides useful prognostic information relative to the time to progression where therapy is required and survival. The presence of del(11q) and/or del(17p) are associated with short progression-free survival to chemotherapy and chemoimmunotherapy approaches. Alemtuzumab or high-dose steroids have response in del(17p) disease.

[b]IGHV rearrangements involving VH3-21 carry a poor prognosis even if mutated.

[c]Formal studies identifying the percentage of abnormal cells identified by FISH are ongoing, although populations less than 10% appear to not have the clinical impact as noted in the table.

[d]Complex karyotype is based on results of conventional karyotyping of stimulated CLL cells.

CSLL-A

CLL STAGING SYSTEMS

Rai System[a]

Stage	Description	Risk Status
0	Lymphocytosis, lymphocytes in blood >15,000/mcL and >40% lymphocytes in the bone marrow	Low
I	Stage 0 with enlarged node(s)	Intermediate
II	Stage 0–I with splenomegaly, hepatomegaly, or both	Intermediate
III[c]	Stage 0–II with hemoglobin <11.0 g/dL or hematocrit <33%	High
IV[c]	Stage 0–III with platelets <100,000/mcL	High

Binet System[b]

Stage	Description
A	Hemoglobin ≥10 g/dL and Platelets ≥100,000/mm^3 and <3 enlarged areas
B	Hemoglobin ≥10 g/dL and Platelets ≥100,000/mm^3 and ≥3 enlarged areas
C[c]	Hemoglobin <10 g/dL and/or Platelets <100,000/mm^3 and any number of enlarged areas

[a] This research was originally published in Blood. Rai KR, Sawitsky A, Cronkite EP, Chanana AD, Levy RN, Pasternack BS. Clinical staging of chronic lymphocytic leukemia. Blood 1975;46(2):219-234. © The American Society of Hematology.
[b] From: Binet JL, Auquier A, Dighiero G, et al. A new prognostic classification of chronic lymphocytic leukemia derived from a multivariate survival analysis. Cancer 1981;48:198-206.
[c] Immune-mediated cytopenias are not the basis for these stage definitions.

CSLL-B

Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma, Version 1.2015

SUPPORTIVE CARE FOR PATIENTS WITH CLL

Recurrent Sinopulmonary Infections (requiring IV antibiotics or hospitalization)	• Antimicrobials as appropriate
	• Evaluate serum IgG, if <500 mg/dL
	  ➤ begin monthly IVIG 0.3–0.5 g/kg,
	  ➤ adjust dose/interval to maintain nadir level of approximately 500 mg/dL

Antiinfective Prophylaxis	• Recommended for patients receiving purine-analog and/or alemtuzumab during treatment and thereafter, if tolerated
	  ➤ Herpes virus (acyclovir or equivalent)
	  ➤ PCP (sulfamethoxazole/trimethoprim or equivalent)
	• Alemtuzumab: Clinicians must be aware of the high risk of CMV reactivation. The current appropriate management is controversial; some use ganciclovir (oral or IV) prophylactically if viremia is present, others use ganciclovir only if viral load is rising. CMV viremia should be measured by PCR quantitation at least every 2–3 wks. Consultation with an infectious disease expert may be necessary.
	
	• Recommend HBV prophylaxis and monitoring in high-risk patients receiving anti-CD20 monoclonal antibodies and alemtuzumab. See Supportive Care for NHL (NHODG-B*) for details on the management of infections.

Autoimmune Cytopenias	• Autoimmune hemolytic anemia (AIHA): Diagnosis with reticulocyte count, haptoglobin, DAT ➤ AIHA that develops in setting of treatment with fludarabine: stop, treat, and avoid subsequent fludarabine • Immune thrombocytopenic purpura (ITP): Evaluate bone marrow for cause of low platelets • Pure red cell aplasia (PRCA): Evaluate for parvo B19 and bone marrow evaluation • Treatment: Corticosteroids, rituximab, IVIG, cyclosporin A, splenectomy, eltrombopag, or romiplostim (ITP)
Vaccination	• Annual influenza vaccine[a] • Pneumococcal vaccine (Prevnar preferred) every 5 yrs • Avoid all live vaccines, including Zoster
Blood Product Support	• Transfuse according to institutional or published standards • Irradiate all blood products to avoid transfusion-associated GVHD

*Available online, in these guidelines, at NCCN.org.

[a] In patients who have received rituximab, B-cell recovery occurs by approximately 9 months. Prior to B-cell recovery, patients generally do not respond to influenza vaccine and if given should not be considered vaccinated.

CSLL-C
1 of 2

SUPPORTIVE CARE FOR PATIENTS WITH CLL

Tumor Lysis Syndrome (TLS)	• Consider tumor prophylaxis measures in patients with bulky disease at high risk for TLS. 　▸ For details on the symptoms, prophylaxis, and management of TLS in NHL, see Supportive Care for NHL (NHODG-B*).
Tumor Flare Reactions	• Management of tumor flare recommended for patients receiving lenalidomide • Tumor flare reactions: 　▸ Painful lymph node enlargement or lymph node enlargement with evidence of local inflammation, occurring with treatment initiation; may also be associated with spleen enlargement, low-grade fever, and/or rash • Treatment: 　▸ Steroids (eg, prednisone 25–50 mg PO for 5–10 days) 　▸ Antihistamines for rash and pruritus (cetirizine 10 mg PO QID or loratadine 10 mg PO daily) • Prophylaxis: 　▸ Consider in patients with bulky lymph nodes (>5 cm) 　▸ Steroids (eg, prednisone 20 mg PO for 5–7 days followed by rapid taper over 5–7 days)
Thromboprophylaxis	• Recommended for prevention of thromboembolic events in patients receiving lenalidomide: 　▸ Aspirin 81 mg daily if platelets above 50×10^{12}/L 　▸ Patients already on anticoagulants, such as warfarin, do not need aspirin • Note that the above may differ from the NCCN Guidelines for Venous Thromboembolic Disease† in which the recommendations with lenalidomide pertain only to patients with multiple myeloma

*Available online, in these guidelines, at NCCN.org.
†To view the most recent version of these guidelines, visit NCCN.org.

CSLL-C
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Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma, Version 1.2015

SUGGESTED TREATMENT REGIMENS[a]
(in order of preference)

CLL without del (11q) or del (17p)

Frail patient, significant comorbidity
(not able to tolerate purine analogs)

- Obinutuzumab + chlorambucil (category 1)
- Ofatumumab + chlorambucil
- Rituximab + chlorambucil
- Obinutuzumab (category 2B)
- Rituximab (category 2B)
- Chlorambucil (category 2B)
- Pulse corticosteroids (category 3)

> See Supportive Care for Patients with CLL (CSLL-C)
>
> Consider prophylaxis for tumor lysis syndrome (See NHODG-B*)
>
> See monoclonal antibody and viral reactivation (NHODG-B*)

First-line therapy[b]

- Age ≥70 y and younger patients with significant comorbidities
  - Obinutuzumab + chlorambucil (category 1)
  - Ofatumumab + chlorambucil
  - Rituximab + chlorambucil
  - Bendamustine (70 mg/m^2 in cycle 1 with escalation to 90 mg/m^2 if tolerated) ± rituximab
  - Obinutuzumab (category 2B)
  - Fludarabine[c,d,e] ± rituximab (category 2B)
  - Chlorambucil (category 2B)
  - Rituximab (category 3)
  - Cladribine (category 3)[f]

- Age <70 y without significant comorbidities
  - Chemoimmunotherapy
    - FCR[c] (fludarabine,[e] cyclophosphamide, rituximab) (category 1)
    - FR[c] (fludarabine,[e] rituximab)
    - PCR (pentostatin, cyclophosphamide, rituximab)
    - Bendamustine ± rituximab

Relapsed/Refractory therapy

See Suggested Regimens for Relapsed/Refractory therapy for CLL without del (11q) or del (17p) (2 of 7)

See Suggested Regimens for CLL with del (17p) (3 of 7)

See Suggested Regimens for CLL with del (11q) (4 of 7)

*Available online, in these guidelines, at NCCN.org.

[a] See references for regimens CSLL-D 6 of 7 and CSLL-D 7 of 7.
[b] See Supportive Care for Patients with CLL (CSLL-C).
[c] Autoimmune hemolytic anemia (AIHA) should not preclude the use of combination therapy containing fludarabine and patients should be observed carefully.
[d] In patients ≥70 y, fludarabine does not have a benefit for first-line therapy over other therapies including chlorambucil.
[e] See Discussion for further information on oral fludarabine.
[f] In rare circumstances of CNS disease, cladribine is potentially useful.

**CSLL-D
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SUGGESTED TREATMENT REGIMENS[a]
(in order of preference)
CLL without del (11q) or del (17p)

Relapsed/Refractory therapy[b]

- Age ≥70 y and younger patients with significant comorbidities
  - ➤ Ibrutinib[g] (category 1)
  - ➤ Idelalisib ± rituximab[g,h]
  - ➤ Chemoimmunotherapy
    - ◇ Reduced-dose FCR[c,e]
    - ◇ Reduced-dose PCR
    - ◇ Bendamustine ± rituximab
    - ◇ High-dose methylprednisolone (HDMP) + rituximab
    - ◇ Rituximab + chlorambucil
  - ➤ Ofatumumab
  - ➤ Obinutuzumab
  - ➤ Lenalidomide[i] ± rituximab
  - ➤ Alemtuzumab[j] ± rituximab
  - ➤ Dose-dense rituximab (category 2B)

- Age <70 y without significant comorbidities
  - ➤ Ibrutinib[g] (category 1)
  - ➤ Idelalisib ± rituximab[g,h]
  - ➤ Chemoimmunotherapy
    - ◇ FCR[c,e]
    - ◇ PCR
    - ◇ Bendamustine ± rituximab
    - ◇ Fludarabine[c,e] + alemtuzumab
    - ◇ RCHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone)
    - ◇ OFAR[c] (oxaliplatin, fludarabine,[e] cytarabine, rituximab)
  - ➤ Ofatumumab
  - ➤ Obinutuzumab
  - ➤ Lenalidomide[i] ± rituximab
  - ➤ Alemtuzumab[j] ± rituximab
  - ➤ HDMP + rituximab

See Supportive Care for Patients with CLL (CSLL-C)

Consider prophylaxis for tumor lysis syndrome (See NHODG-B*)

See monoclonal antibody and viral reactivation (NHODG-B*)

See Suggested Regimens for CLL with del (17p) (3 of 7)

See Suggested Regimens for CLL with del (11q) (4 of 7)

*Available online, in these guidelines, at NCCN.org.

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[a] See references for regimens CSLL-D 6 of 7 and CSLL-D 7 of 7.
[b] See Supportive Care for Patients with CLL (CSLL-C).
[c] Autoimmune hemolytic anemia (AIHA) should not preclude the use of combination therapy containing fludarabine and patients should be observed carefully.
[e] See Discussion for further information on oral fludarabine.
[g] See Special Considerations for Use of B-Cell Receptor Inhibitors (Ibrutinib and Idelalisib) (NHODG-E*).

[h] Indicated for patients for whom rituximab monotherapy would be considered appropriate due to the presence of other comorbidities (reduced renal function as measured by creatinine clearance <60 mL/min, or NCI CTCAE Grade ≥3 neutropenia or Grade ≥3 thrombocytopenia resulting from myelotoxic effects of prior therapy with cytotoxic agents.)
[i] Lenalidomide can be given as continuous or intermittent dosing for patients with CLL. Growth factors and/or dose adjustment may be needed to address cytopenias, without necessitating holding treatment. See Badoux XC, Keating MJ, O'Brien SM, et al. Blood 2011;118:Abstract 980. Badoux XC, Keating MJ, Wen S, et al. Blood 2011;118:3489-3498. Chanan-Khan A, Miller KC, Musial L, et al. J Clin Oncol 2006;24:5343-5349.
[j] While alemtuzumab is no longer commercially available for CLL, it may be obtained for clinical use. Less effective for bulky (>5 cm) lymphadenopathy; monitor for CMV reactivation.

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Clinical trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged. All recommendations are category 2A unless otherwise indicated.

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SUGGESTED TREATMENT REGIMENS[a]
(in order of preference)

CLL with del (17p)

<u>First-line therapy[b]</u>
- Ibrutinib[g]
- HDMP + rituximab
- FCR[c,e]
- FR[c,e]
- Obinutuzumab + chlorambucil
- Alemtuzumab[j] ± rituximab

<u>Relapsed/Refractory therapy[b]</u>
- Ibrutinib[g]
- Idelalisib ± rituximab[g,h]
- HDMP ± rituximab
- Lenalidomide[i] ± rituximab
- Alemtuzumab[j] ± rituximab
- Ofatumumab[k]
- OFAR[c,e]

See Supportive Care for Patients
with CLL (CSLL-C)

Consider prophylaxis for tumor lysis
syndrome (See NHODG-B*)

See monoclonal antibody and viral
reactivation (NHODG-B*)

See Suggested Regimens for CLL without del (11q) or del (17p) (1 of 7)

See Suggested Regimens for CLL with del (11q) (4 of 7)

*Available online, in these guidelines, at NCCN.org.

[a] See references for regimens CSLL-D 6 of 7 and CSLL-D 7 of 7.
[b] See Supportive Care for Patients with CLL (CSLL-C).
[c] Autoimmune hemolytic anemia (AIHA) should not preclude the use of combination therapy containing fludarabine and patients should be observed carefully.
[e] See Discussion for further information on oral fludarabine.
[g] See Special Considerations for Use of B-Cell Receptor Inhibitors (Ibrutinib and Idelalisib) (NHODG-E*).

[h] Indicated for patients for whom rituximab monotherapy would be considered appropriate due to the presence of other co-morbidities (reduced renal function as measured by creatinine clearance <60 mL/min, or NCI CTCAE Grade ≥3 neutropenia or Grade ≥3 thrombocytopenia resulting from myelotoxic effects of prior therapy with cytotoxic agents.)
[i] Lenalidomide can be given as continuous or intermittent dosing for patients with CLL. Growth factors and/or dose adjustment may be needed to address cytopenias, without necessitating holding treatment. See Badoux XC, Keating MJ, O'Brien SM, et al. Blood 2011;118:Abstract 980. Badoux XC, Keating MJ, Wen S, et al. Blood 2011;118:3489-3498. Chanan-Khan A, Miller KC, Musial L, et al. J Clin Oncol 2006;24:5343-5349.
[j] While alemtuzumab is no longer commercially available in CLL, it may be obtained for clinical use. Less effective for bulky (>5 cm) lymphadenopathy; monitor for CMV reactivation.
[k] This is not effective in patients with lymph nodes >5 cm.

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SUGGESTED TREATMENT REGIMENS[a]
(in order of preference)

CLL with del (11q)

First-line therapy[b]

- Age ≥70 y and younger patients with significant comorbidities
  ➤ Obinutuzumab + chlorambucil (category 1)
  ➤ Ofatumumab + chlorambucil (category 2A)
  ➤ Rituximab + chlorambucil
  ➤ Bendamustine (70 mg/m^2 in cycle 1 with escalation to 90 mg/m^2 if tolerated) ± rituximab
  ➤ Cyclophosphamide, prednisone ± rituximab
  ➤ Reduced-dose FCR[c,d,e]
  ➤ Chlorambucil
  ➤ Rituximab (category 3)

- Age <70 y without significant comorbidities
  ➤ Chemoimmunotherapy
    ◇ FCR[c,e]
    ◇ Bendamustine ± rituximab
    ◇ PCR
    ◇ Obinutuzumab + chlorambucil

Relapsed/Refractory therapy[b]

See Suggested Regimens for Relapsed/Refractory therapy for CLL with del (11q) (5 of 7)

See Supportive Care for Patients with CLL (CSLL-C)

Consider prophylaxis for tumor lysis syndrome (See NHODG-B*)

See monoclonal antibody and viral reactivation (NHODG-B*)

See Suggested Regimens for CLL without del (11q) or del (17p) (1 of 7)

See Suggested Regimens for CLL with del (17p) (3 of 7)

*Available online, in these guidelines, at NCCN.org.

[a] See references for regimens CSLL-D 6 of 7 and CSLL-D 7 of 7.
[b] See Supportive Care for Patients with CLL (CSLL-C).
[c] Autoimmune hemolytic anemia (AIHA) should not preclude the use of combination therapy containing fludarabine and patients should be observed carefully.
[d] In patients ≥70 y, fludarabine does not appear to have a benefit for first-line therapy over other therapies including chlorambucil.
[e] See Discussion for further information on oral fludarabine.

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Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma, Version 1.2015

SUGGESTED TREATMENT REGIMENS[a]
(in order of preference)
CLL with del (11q)

Relapsed/Refractory therapy[b]

- Age ≥70 y and younger patients with significant comorbidities
  - ‣ Ibrutinib[g] (category 1)
  - ‣ Idelalisib ± rituximab[g,h]
  - ‣ Chemoimmunotherapy
    - ⬥ Reduced-dose FCR[c,e]
    - ⬥ Reduced-dose PCR
    - ⬥ Bendamustine ± rituximab
    - ⬥ HDMP + rituximab
    - ⬥ Rituximab + chlorambucil
  - ‣ Ofatumumab
  - ‣ Obinutuzumab
  - ‣ Lenalidomide[i] ± rituximab
  - ‣ Alemtuzumab[j] ± rituximab
  - ‣ Dose-dense rituximab (category 2B)

- Age <70 y without significant comorbidities
  - ‣ Ibrutinib[g] (category 1)
  - ‣ Idelalisib ± rituximab[g,h]
  - ‣ Chemoimmunotherapy
    - ⬥ FCR[c,e]
    - ⬥ PCR
    - ⬥ Bendamustine ± rituximab
    - ⬥ Fludarabine[c,e] + alemtuzumab
    - ⬥ OFAR[c,e]
  - ‣ Ofatumumab
  - ‣ Obinutuzumab
  - ‣ Lenalidomide[i] ± rituximab
  - ‣ Alemtuzumab[j] ± rituximab
  - ‣ HDMP + rituximab

See Supportive Care for Patients with CLL (CSLL-C)

Consider prophylaxis for tumor lysis syndrome (See NHODG-B*)

See monoclonal antibody and viral reactivation (NHODG-B*)

See Suggested Regimens for CLL without del (11q) or del (17p) (1 of 7)

See Suggested Regimens for CLL with del (17p) (3 of 7)

*Available online, in these guidelines, at NCCN.org.

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[a] See references for regimens CSLL-D 6 of 7 and CSLL-D 7 of 7.
[b] See Supportive Care for Patients with CLL (CSLL-C).
[c] Autoimmune hemolytic anemia (AIHA) should not preclude the use of combination therapy containing fludarabine and patients should be observed carefully.
[e] See Discussion for further information on oral fludarabine.
[g] See Special Considerations for Use of B-Cell Receptor Inhibitors (Ibrutinib and Idelalisib) (NHODG-E*).

[h] Indicated for patients for whom rituximab monotherapy would be considered appropriate due to the presence of other co-morbidities (reduced renal function as measured by creatinine clearance <60 mL/min, or NCI CTCAE Grade ≥3 neutropenia or Grade ≥3 thrombocytopenia resulting from myelotoxic effects of prior therapy with cytotoxic agents.)
[i] Lenalidomide can be given as continuous or intermittent dosing for patients with CLL. Growth factors and/or dose adjustment may be needed to address cytopenias, without necessitating holding treatment. See Badoux XC, Keating MJ, O'Brien SM, et al. Blood 2011;118:Abstract 980. Badoux XC, Keating MJ, Wen S, et al. Blood 2011;118:3489-3498. Chanan-Khan A, Miller KC, Musial L, et al. J Clin Oncol 2006;24:5343-5349.
[j] While alemtuzumab is no longer commercially available in CLL, it may be obtained for clinical use. Less effective for bulky (>5 cm) lymphadenopathy; monitor for CMV reactivation.

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RESPONSE DEFINITION AFTER TREATMENT FOR CLL[a,b]

Parameter	Complete Response	Partial Response	Progressive Disease
Group A			
Lymphadenopathy[†]	None >1.5 cm	Decrease ≥50%	Increase ≥50%
Hepatomegaly	None	Decrease ≥50%	Increase ≥50%
Splenomegaly	None	Decrease ≥50%	Increase ≥50%
Marrow[‡]	Normocellular, <30% lymphocytes, no B-lymphoid nodules; hypocellular marrow defines CR with incomplete marrow recovery (CRi)	50% reduction in marrow infiltrate, or B-lymphoid nodules	
Blood lymphocytes	<4000/µL	Decrease ≥50% over baseline	Increase ≥50% over baseline[b]
Group B			
Platelet count without growth factors	>100,000/µL	>100,000/µL or increase ≥50% over baseline	Decrease ≥50% over baseline secondary to CLL
Hemoglobin without transfusions or growth factors	>11.0 g/dL	>11 g/dL or increase ≥50% over baseline	Decrease of >2 g/dL from baseline secondary to CLL
Neutrophils without growth factors[‡]	>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).
Complete remission (CR): all of the criteria have to be met, and patients have to lack disease-related constitutional symptoms.
Partial remission (PR): Requires 1) having two of the group A criteria if 2 or more are present. Patients with one group A criteria (excluding bone marrow) are also considered evaluable for response; 2) one group B criteria whether or not normal from baseline prior to starting therapy.
Stable disease is absence of progressive disease (PD) and failure to achieve at least a PR.
PD: appearance of any new lesions; 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.
[a]Hallek M, Cheson BD, Catovsky D, et al. 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. Blood 2008;111:5446-5456.
[b]Isolated progressive lymphocytosis in the setting of reduced lymph node size or organomegaly or improvement in hemoglobin/platelets will not be considered progressive disease.

CSLL-E

Clinical trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged. All recommendations are category 2A unless otherwise indicated.

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Text cont. from page 327.

ria for CLL.[5] Favorable molecular lesions, mutated immunoglobulin heavy-chain variable region gene (*IGHV*) and chromosomal abnormality del(13q) or normal cytogenetics are commonly seen in individuals with MBL.[6] The estimated rate of progression of MBL to CLL is 1.1% per year.[6]

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for NHL now include an initial stratification between CLL/SLL and MBL (absolute B-lymphocyte count of <5000/mm^{3}, lymph nodes <1.5 cm, no thrombocytopenia or anemia). Observation is recommended for all individuals with MBL. (To view the most recent and complete version of these guidelines, visit NCCN.org.) The diagnosis of CLL requires the presence of at least 5000 monoclonal B lymphocytes/mcL (5 x 10^{9}/L) in peripheral blood and the clonality of B cells should be confirmed by flow cytometry. The diagnosis of SLL requires the presence of lymphadenopathy and/or splenomegaly, with less than 5000 B lymphocytes/mcL (5 x 10^{9}/L) in the peripheral blood.[3] B cells with a CLL/SLL phenotype may be found in samples from patients with reactive lymph nodes; however, a diagnosis of SLL should only be made when effacement of the lymph node architecture is observed in biopsy samples.

Adequate immunophenotyping is essential to establish the diagnosis of CLL/SLL. Flow cytometry of peripheral blood is adequate for the diagnosis of CLL, and bone marrow biopsy is generally not required. A diagnosis of SLL should ideally be confirmed with the evaluation of lymph node biopsy samples. Cell surface markers for flow cytometric studies should include kappa/lambda, CD19, CD20, CD5, CD23, and CD10. If flow cytometry is used to establish a diagnosis, flow evaluation for cyclin D1 or fluorescence in situ hybridization (FISH) analysis for t(11;14) should also be included to rule out mantle cell lymphoma (MCL). Paraffin-section immunohistochemistry (IHC) on excisional or incisional lymph node biopsy materials can be performed if a diagnosis is not established by flow cytometry. Recommended IHC panels include CD3, CD5, CD10, CD20, CD23, and cyclin D1. These can be useful, particularly for diagnosing CLL/SLL type without circulating leukemic cells.

The typical immunophenotype for CLL/SLL is CD5+, CD10-, CD19+, and CD20 dim, surface immunoglobulin dim, CD23+, CD43+/-, and cyclin D1-. Distinguishing CLL/SLL from MCL is essential, as they are both CD5+ B-cell tumors. Although CD23 is often helpful, absence of cyclin D1 expression is critical in this differentiation of tumor types. Stimulated cytogenetics or FISH analysis for t(11;14) can help to distinguish MCL from CLL and should be performed if flow cytometry alone is used to evaluate immunophenotype. FISH for the detection of del(11q), del(13q), trisomy 12, and del(17p), and stimulated metaphase karyotype and molecular genetic analysis (by PCR or sequencing) to detect *IGHV* mutation status and *TP53* mutations can provide useful prognostic information and may guide selection of therapy. Recent reports suggest that complex karyotype (≥3 unrelated chromosomal abnormalities in more than one cell on conventional karyotyping of stimulated CLL cells) is associated with an unfavorable prognosis.[7–9] Cytogenetic abnormalities can evolve over time; therefore, reevaluation of FISH and karyotype is necessary to direct treatment options in patients with indications for treatment.

Conventional metaphase cytogenetics is difficult in CLL as a result of the very low in vitro proliferative activity of the leukemic cells. Therefore, interphase cytogenetic analysis with FISH is the standard method to detect chromosomal abnormalities that may have prognostic significance. However, FISH can only detect abnormalities specific to the probes used. Cytokine or CpG oligonucleotide stimulation was used to enhance metaphase analysis.[10] Recent studies demonstrated that stimulation with CpG oligonucleotide and interleukin-2 is more effective than with 12-O-tetradecanoylphorbol-13-acetate (TPA) for the detection of chromosomal abnormalities in CLL.[11,12] A prospective study conducted by the CLL Research Consortium confirmed that abnormal clones in CLL are more readily detected with CpG oligonucleotide stimulation than with traditional B-cell mitogens; moreover, the clonal abnormalities revealed by CpG stimulated metaphase cytogenetics are consistent with that detected by interphase FISH and are reproducible among different cytogenetic laboratories.[13] However, the use of CpG stimulation for CLL cytogenetics is not yet universally available.

Prognostic Factors

During the past decade, numerous factors were identified and evaluated in patients with CLL that may provide useful prognostic information beyond

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clinical staging (see "Staging," page 350). These factors include serum markers such as thymidine kinase and beta-2 microglobulin, genetic markers including *IGHV* mutational status, and cytogenetic abnormalities detected by FISH (eg, del(13q), del(11q), del(17p)), CD38 expression, CD49d and zeta-associated protein 70 (ZAP-70) expression/methylation).[14–26]

IGHV mutational status is an important predictor of survival outcomes in CLL; unmutated *IGHV* (≥98% homology with germline gene sequence) is associated with poor prognosis and significantly decreased survival compared with mutated *IGHV*, irrespective of the stage of the disease.[15,20] In addition, *VH3-21* gene usage was associated with poor outcomes regardless of the mutation status (as defined by percent homology with germline sequence).[27] Unmutated *IGHV* or the use of *VH3-21* was shown to be independent predictors of shorter treatment-free interval and/or survival outcomes, even when high-risk genomic abnormalities were included in the multivariable regression models (see subsequent discuss of cytogenetic abnormalities detected by FISH).[28–31]

Expression of CD38 (≥7% of B lymphocytes)[15,16,22,29,30,32] and/or ZAP-70 (≥20% of B lymphocytes)[14,23–25,33] were also associated with shorter progression-free survival (PFS) and overall survival (OS) outcomes. Among the flow cytometry–based prognostic assays (CD38, ZAP-70, and CD49d), CD49d appears to be the strongest prognostic parameter and is the only one that is independent of FISH and *IGHV*.[26] Both CD38 and ZAP-70 positivity correlate with unmutated *IGHV*, and were suggested as potential surrogate markers for *IGHV* mutational status.[14,15,25] However, discordant results between CD38 positivity and *IGHV* mutational status were seen in up to 28% of patients in one study; moreover, CD38 expression levels may vary over the course of the disease.[21] Similarly, discordant results between ZAP-70 positivity and *IGHV* mutational status were reported in 20% to 25% of cases.[24,30]

In addition, ZAP-70 positivity was suggested to be a stronger predictor of outcomes (eg, time to first treatment) than *IGHV* mutational status or CD38 levels.[24,33,34] ZAP-70 methylation analysis (which is closely associated with ZAP-70 expression and *IGHV* mutational status) was also reported to be a useful prognostic test for patients with CLL.[35–37]

CD38 and/or ZAP-70 expressions can be determined using IHC, flow cytometry, or methylation. However, standardization and reproducibility of ZAP-70 expression across laboratories remains a challenge. Evaluation of ZAP-70 protein expression is not recommended outside the context of clinical trials. Therefore, in clinical practice, *IGHV* mutation testing is recommended based on reproducibility and ready availability.

An elevated serum beta-2 microglobulin level was shown to be a strong independent prognostic indicator for treatment-free interval, response to treatment, and OS, including in patients treated with first-line chemoimmunotherapy regimens.[38–40] One of the advantages of beta-2 microglobulin is that it is readily measured by standard laboratory evaluation of blood samples. However, it is influenced in a CLL disease–independent manner by renal dysfunction. Wierda et al[41] developed a prognostic nomogram using clinical and laboratory parameters that are available in the routine clinical practice setting (age, beta-2 microglobulin, absolute lymphocyte count, sex, Rai stage, and number of involved lymph nodes); the nomogram was developed to estimate the median survival time, and the probability of 5- and 10-year survival.

In addition, based on the sum of points assigned to the 6 parameters used for the nomogram, a more simplified prognostic index was developed to help stratify untreated patients with CLL into 3 different risk groups (low, intermediate, and high).[41] The estimated median survival was not reached for the low-risk group. The median survival times for intermediate- and high-risk groups were 10 and 5 years, respectively. The 5-year survival rates were 97% for low-risk, 80% for intermediate-risk, and 55% for high-risk groups; the 10-year survival rates were 80%, 52%, and 26%, respectively.[41] It should be noted that sufficient data were not available for recently identified prognostic factors (eg, *IGHV* mutational status, ZAP-70, cytogenetic abnormalities detected by FISH) to be incorporated into this version of the prognostic model. Nevertheless, several studies independently confirmed the utility of this prognostic index in estimating both survival probability and time to first treatment in previously untreated patients with CLL, including in patients with early-stage (Rai stage 0) disease.[42,43]

Cytogenetic abnormalities that can be detected

by FISH are present in more than 80% of patients with previously untreated CLL. FISH is categorized according to the highest-risk abnormality present, according to a hierarchical categorization. The most common abnormality is del(13q) (55%) as a sole finding, followed by del(11q) (18%), trisomy 12 (16%), del(17p) (7%), and del(6q) (7%).[17] As a sole abnormality, del(13q) is associated with favorable prognosis and the longest median survival (133 months), whereas del(11q) is often associated with extensive lymphadenopathy, disease progression, and shorter median survival (79 months).[17,44] Among patients with del(11q), those with a complete loss of ATM function might have impaired response to irradiation or cytotoxic drugs, resulting in poor clinical outcome.[45] Recent studies showed that previously untreated patients with del(11q) respond well to combination therapy with fludarabine and cyclophosphamide (FC), suggesting that the addition of an alkylating agent to fludarabine may help to overcome the adverse prognostic significance of del(11q) in patients with CLL.[30,46] Del(17p), which reflects the loss of the TP53 gene and is frequently associated with mutations in the remaining TP53 allele, is associated with worst outcomes, with short treatment-free interval, short median survival (32 months), and poor response to chemotherapy.[17]

The phase III randomized CLL8 study of the German CLL Study Group (GCLLSG; first-line FC vs rituximab combined with FC [FCR]) showed that both del(17p) and unmutated IGHV were significant independent predictors of poor survival outcomes, irrespective of the treatment arm.[47] Although FCR was associated with significantly improved PFS among patients with del(17p), the 3-year PFS rate was only 18% in this subgroup. In addition, OS outcomes in patients with del(17p) were similar between the FCR and FC arms (3-year OS, 38% and 37%, respectively).[47] The prognostic importance of del(17p) may be dependent on the proportion of malignant cells with this abnormality. In the UK LRF CLL4 trial (comparing first-line therapy with chlorambucil vs fludarabine vs FC), similar outcomes were seen between patient subgroups with 5% to 10% of cells with TP53 deletion (ie, del(17p13.1)) and the subgroup without TP53 deletion (deletion in <5% of cells); patients with 10% to 20% TP53 deletion had outcomes similar to those with more than 20% TP53 deletion.[30,48] Patients with 10% or

more cells with TP53 deletion had a poor outcome, with a 29% response rate (6% complete or nodular partial response) and a median survival of less than 6 months.[30] The finding that del(17p) is more frequently seen in treated than in untreated patients suggests that treatment-driven clonal selection may occur during therapy. Indeed, acquisition and/or expansion of CLL clones with del(17p) were observed during the course of treatment.[49]

A prognostic nomogram for estimating time to first treatment was developed based on a multivariable model that included both traditional clinical and laboratory parameters and newer prognostic factors (eg, FISH cytogenetics, IGHV mutational status, and ZAP-70 expression levels).[50] The following factors were identified as independent predictors of shorter time to first treatment and were included in a weighted model to estimate the probability of treatment (at 2 and 4 years) and time to first treatment: increased size of cervical lymph nodes, 3 involved nodal sites, del(17p) or del(11q), unmutated IGHV status, and elevated serum LDH levels.[50] This nomogram may help to identify newly diagnosed patients at high risk for disease progression who may require earlier intervention. More recently, the GCLLSG developed a comprehensive prognostic index to stratify patients into 4 risk groups based on OS. In this model, sex, age, ECOG status, del(17p), del(11q), IGHV mutation status, serum beta-2 microglobulin, and serum thymidine kinase were identified as independent predictors of OS in newly diagnosed patients.[51]

Abnormalities of TP53 can be observed in the absence of del(17p).[52,53] Studies with fludarabine-based regimens identified TP53 mutations as an independent predictor of decreased survival and resistance to chemotherapy.[52–55] Resistance to chemotherapy was attributed to the presence of mutation in the remaining TP53 allele.[53] Thus, the presence of TP53 mutation predicts for poor survival outcomes independent of 17p chromosome status.[52] In an analysis from the CLL8 study, mutation in TP53 was associated with significantly decreased PFS and OS outcomes regardless of treatment with FCR or FC.[53]

The impact of these prognostic factors on the clinical outcome of patients was examined in large prospective randomized studies. In the long-term follow up from the CALGB 9712 study (first-line therapy with concurrent vs sequential fludarabine and rituximab), unmutated IGHV was a significant

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independent predictor for shorter PFS and OS, while poor-risk cytogenetic abnormalities (ie, del(17p) or del(11q)) remained an independent predictor for shorter survival.[56] In the UK LRF CLL4 trial, *TP53* loss was found to be the strongest predictor of poor outcomes.[30,54] Among the subgroup of patients without *TP53* loss, unmutated *IGHV* (or *VH3-21* usage) and elevated beta-2 microglobulin (>4 mg/L) were significant independent predictors for both PFS and OS outcomes.[30] In addition, del(11q) and treatment allocation were independent predictors for PFS, and age was an independent predictor for OS. In the German CLL8 trial (first-line FC vs FCR), mutated *TP53*, del(17p), unmutated *IGHV*, and treatment arm were significant independent prognostic factors for both PFS and OS outcomes.[53]

During the past few years, recurrent mutations in *NOTCH1, SF3B1,* and *BIRC3* genes with prognostic implications in CLL were identified.[53,57–65] *NOTCH1* mutation was also independently associated with Richter's transformation.[66,67] The impact of these mutations relative to treatment with newer targeted therapies is uncertain. Collectively, the previously discussed studies suggest that the prognostic significance of these mutations may vary depending on the patient population, treatment regimens, and clinical outcomes being evaluated. Although these prognostic factors may provide useful prognostic information, treatment initiation or selection of treatment options should not be driven by these factors. Moreover, in the general clinical practice setting, prognostic factors should not determine treatment choices, with the exception of del(17p) or del(11q).

Workup

The workup for CLL/SLL is similar to that for other lymphoid neoplasms. Quantitative immunoglobulins may be informative in patients with recurrent infections. Measurement of beta-2 microglobulin may provide useful prognostic information.[39,41] Though the pattern of bone marrow involvement (diffuse vs nodular) had prognostic significance classically, this is no longer a factor when one uses more reliable prognostic markers such as *IGHV* mutational status and cytogenetic abnormalities determined by FISH, all of which can be obtained by analysis of circulating lymphocytes. Thus, bone marrow biopsy is no longer considered a required part of the diagnostic evaluation of patients with suspected CLL, though it remains useful to evaluate the etiology of cytopenias.

CT scans may be useful to follow and monitor disease progression in patients with new symptoms when peripheral adenopathy is not present. For asymptomatic patients, serial CT scans are not recommended. For patients with anemia, reticulocyte counts and a direct Coombs' test should be performed to evaluate for the possibility of hemolysis and pure red aplasia. PET scan is generally not useful in CLL, but it can assist in directing nodal biopsy if Richter's transformation is suspected.[68,69] Bone marrow biopsy with or without aspirate could be useful in ceratin circumstances before starting treatment.

Staging

Two staging systems, Rai and Binet, are currently used worldwide in the evaluation of patients with CLL in both routine practice and clinical trial settings.[70,71] Both staging systems rely solely on physical examination (presence of lymph node involvement, enlarged spleen and/or liver) and blood parameters (presence of anemia or thrombocytopenia) to assess the degree of tumor burden. The modified Rai classification stratifies patients into 3 risk groups (low, intermediate, high). Survival of patients with low-risk disease (Rai stage 0; median survival, 150 months) is essentially the same as the survival rate of age-matched controls. Patients with intermediate-risk disease (Rai stage, I–II; median survival, 71–101 months) have shorter survival, particularly when other adverse factors coexist, such as a lymphocyte doubling time of less than 1 year. Patients with high-risk features (Rai stage, III–IV; median survival, 19 months) have poor prognosis.[70] The Binet staging system is based on the number of involved areas and the level of hemoglobin and platelets. Similar to the Rai staging system, it provides meaningful correlation with clinical outcome.[71] The nearly universal involvement of bone marrow and peripheral blood in CLL/SLL limits the utility of the Ann Arbor staging system.

Response Criteria

The NCI-sponsored Working Group (NCI-WG) on CLL published guidelines for the diagnosis and management of CLL in 1988 and 1996, primarily to facili-

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tate consistency in the design and conduct of clinical trials. Most clinical trials of CLL reporting response outcomes have, until very recently, used the response criteria set forth in the 1996 NCI-WG guidelines.[72] In 2008, the NCI-WG guidelines were revised to reflect recent advances in the understanding of newer prognostic markers, diagnostic parameters, and treatments.[3] In particular, the 2008 guidelines provide further recommendations on the evaluations and response assessments appropriate for the general clinical practice setting versus for clinical trials.[3]

In the clinical practice setting, response assessment involves both physical examination and evaluation of blood parameters. For a complete response (CR), all of the following criteria must be met (at least 2 months after treatment completion): peripheral blood lymphocyte counts less than $4 \times 10^9/L$; absence of lymphadenopathy (ie, palpable nodes must be ≤1.5 cm in diameter); absence of splenomegaly or hepatomegaly; absence of constitutional symptoms (ie, weight loss, significant fatigue, fevers, night sweats); and normalization of blood counts without growth factor support (ie, neutrophils $>1.5 \times 10^9/L$, platelets $>100 \times 10^9/L$, hemoglobin >11 g/dL).[3] For a partial response (PR), at least 2 of the following criteria must be met for at least 2 months: at least 50% reductions from baseline in peripheral blood lymphocyte counts, lymphadenopathy (based on sum of the products of multiple affected nodes), hepatomegaly, and/or splenomegaly; in addition, at least 1 of the blood counts should be normalized or increased by 50% or more from baseline for at least 2 months duration.

Progressive disease comprises any of the following: at least 50% increase from baseline in lymphocyte counts, lymphadenopathy, hepatomegaly, or splenomegaly, and appearance of any new lesions or occurrence of cytopenias attributable to disease (ie, ≥50% decrease from baseline in platelet count, >2 g/dL decrease from baseline in hemoglobin levels).[3] Patients who do not have progressive disease but do not meet the criteria for a CR or PR are considered to have stable disease. Relapse is defined as evidence of disease progression 6 months or more after an initial CR or PR. Refractory disease is defined as failure to experience a response or experiencing disease progression within 6 months of the last treatment.[3]

CT scans are desirable in clinical trials for evaluation of adenopathy and organ involvement and to select patients outside of trials. In addition, a bone marrow evaluation should be conducted to confirm a CR (<30% lymphocytes, normocellular morphology, absence of lymphoid nodules) if all other criteria for clinical CR (as defined previously) are met. Patients who fulfill the criteria for CR (including evaluation of the bone marrow) but present with persistent cytopenias due to treatment-related toxicities should be considered to have experienced a CR with incomplete marrow recovery (CRi).[3]

These response criteria were recently revised to more precisely predict outcomes for patients with CLL treated with immunomodulating agents and small molecule kinase inhibitors.[73] Treatment with immunomodulating agents such as lenalidomide results in a tumor flare reaction characterized by painful enlargement of lymph nodes and lymphocytosis, rash, and bone pain. Tumor flare reaction was correlated with clinical response in patients with CLL treated with lenalidomide.[74] Similarly, the use of small molecule kinase inhibitors (ibrutinib and idelalisib) was known to result in an initial transient increase in lymphocytosis resulting from the redistribution or release of leukemic cells from the lymph node compartment to the peripheral blood.[75,76] In most patients treated with ibrutinib, lymphocytosis resolves within 8 months, but in a subgroup of patients lymphocytosis lasts for more than 12 months. Prolonged lymphocytosis after ibrutinib treatment was reported to represent the persistence of a quiescent clone and does not predict a subgroup of patients likely to relapse early.[77]

Considering these findings, for patients receiving idelalisib and ibrutinib, the revised response criteria recently proposed by Cheson et al[73] allow for a new response category, "PR with lymphocytosis," to include patients with a clinical response (reduction in lymph nodes and splenomegaly) with persistent lymphocytosis (in the absence of other indicators of progressive disease).[73]

Minimal residual disease (MRD) negativity determined in the peripheral blood after the end of treatment is emerging as an important predictor of treatment efficacy. In the combined analysis of 2 phase III GCLLSG studies, among patients who achieved CR, there was a statistically significant difference in PFS between MRD-negative and MRD-positive patients (69.2 vs 40.4 months; P=.001).[78] The persistence of posttreatment splenomegaly as a

sole abnormality in MRD-negative patients had no negative influence on PFS. These results support the use of MRD for response evaluation.

Treatment Options

During the past several decades, therapeutic options for CLL have evolved from the use of alkylating agent monotherapy to purine analog-based combination regimens. The advent of monoclonal antibodies that target cell surface antigens (eg, CD20, CD52) and immunomodulating agents (eg, lenalidomide) led to the development of new and effective combination chemoimmunotherapy regimens. More recently, a number of critical signaling pathways, including the B-cell receptor (BCR), CXCR4/5, CD40, integrin, and IL-6, that signal via phosphatidylinositol 3-kinase (PI3K), Bruton's tyrosine kinase (BTK), and/or spleen tyrosine kinase are implicated in the pathogenesis of CLL.[79,80] Novel small molecule inhibitors targeting these kinases have been evaluated in clinical trials for the treatment of patients with CLL.

This section describes the role of recently approved targeted therapies for the management of patients with CLL/SLL.

First-Line Therapy

Obinutuzumab is a glycoengineered, humanized type II antibody targeted against CD20. The safety and efficacy of obinutuzumab in combination with chlorambucil for previously untreated CLL in patients with coexisting conditions was evaluated in the phase III randomized trial (CLL11 trial).[81] In this trial, 781 patients with comorbidities (defined as Cumulative Illness Rating Score [CIRS] >6 or an estimated creatinine clearance [CrCl] of 30 to 69 mL/min) were randomized to receive chlorambucil (n=118), obinutuzumab plus chlorambucil (n=333) or rituximab plus chlorambucil (n=330). The combinations of obinutuzumab-chlorambucil and of rituximab-chlorambucil resulted in significant improvement in the median PFS compared with chlorambucil alone (26.7, 16.3, and 11.1 months, respectively; $P<.001$). The survival benefit was seen in all of the subgroups except in patients with del(17p). The combination of obinutuzumab plus chlorambucil also resulted in higher overall response rate (ORR, 78.4% vs 65.1%) and CR rate (20.7% vs 7.0%) and significantly prolonged median PFS (26.7 vs 15.2 months; $P<.001$)

compared with rituximab plus chlorambucil.[81] The most frequent grade 3 or higher toxicities with obinutuzumab-chlorambucil included neutropenia (35%), infusion-related reactions (21%), thrombocytopenia (11%), and infections (11%).[81] The most frequent grade 3 or higher toxicities with rituximab plus chlorambucil included neutropenia (28%) and infections (14%). The results of the CLL11 study established obinutuzumab plus chlorambucil as the new standard of care for both elderly patients and for patients with comorbid conditions lacking del(17p).[81] Based on the results of this study, obinutuzumab in combination with chlorambucil was FDA approved for the treatment of untreated CLL/SLL.

The efficacy of obinutuzumab monotherapy in patients with untreated CLL was demonstrated in the phase II GAGE study.[82] In this trial, 80 patients with intact organ function and ECOG performance status less than 3 were stratified to 2 different obinutuzumab doses (1000 vs 2000 mg). The median age was 67 years. Obinutuzumab at 2000 mg resulted in higher ORR (assessed at 2 months after treatment according to the International Workshop on CLL criteria) than obinutuzumab at 1000 mg (67% and 49%, respectively; $P=.08$).[82] Infusion-related reaction was the most frequent grade 3 or 4 adverse event in both treatment arms. Additional studies are warranted to determine the durability of response and long-term adverse effects of obinutuzumab monotherapy in patients with untreated CLL.

Ofatumumab, a fully human CD20 monoclonal antibody, initially approved for the treatment of CLL refractory to fludarabine and alemtuzumab, was also evaluated as a first-line treatment for patients with untreated CLL who were considered inappropriate for fludarabine-based therapy due to advanced age and/or comorbidities.[83] In a multicenter open-label phase III study, 447 patients were randomized to receive ofatumumab plus chlorambucil or chlorambucil monotherapy. With a median follow-up of 29 months, the PFS was significantly longer for patients treated with ofatumumab plus chlorambucil compared with chlorambucil monotherapy (22.4 vs 13.1 months; $P<.001$).[83] Ofatumumab plus chlorambucil also resulted in higher ORR (82% vs 69%; $P=.001$) and superior CR rate (12% vs 1%) compared with chlorambucil alone. The median OS was reached in both arms. Based on the results of this study, the FDA approved ofatumumab plus chlorambucil for

the treatment of previously untreated patients with CLL for whom fludarabine-based therapy is considered inappropriate.

Ibrutinib is a covalent-binding, irreversible inhibitor of BTK, initially approved for relapsed or refractory CLL. It was also evaluated in patients with untreated CLL, including those with del(17p).[84–86] In an open-label multicenter phase Ib/II study of patients over the age of 65 (n=31; median age, 71 years [range, 65–84]; 74% of patients were ≥70 years of age, ibrutinib (420 mg) resulted in an ORR of 71% (13% CR, 3% nodular PR, and 55% PR).[84] The median follow-up was 22 months. The responses were independent of the presence of high-risk features; however, the frequency of patients with del(17p), del(11q), or elevated beta-2 microglobulin was relatively low in this study.[84] The ORR of 84% as reported in an independent evaluation of efficacy data at 3 years after the start of therapy confirmed the durability of responses with ibrutinib in untreated CLL.[85]

In another open-label study of 29 patients (15 treatment-naïve patients) with del (17p), ibrutinib resulted in a nodal response rate of 82% at 6 months in treatment-naïve patients.[86] The median follow-up was 9 months. Grade 3 or higher non-hematologic toxicities were reported in 14% of patients. Ibrutinib was recently approved for first-line treatment of patients with del(17p). Unlike chemotherapy, ibrutinib causes early mobilization of lymphocytes into the blood, which in the setting of clinical improvement should not be mistaken for progressive disease.[72,77] Although lymphocytosis can sometimes be profound, clinical consequence (ie, leukostasis) is extremely rare, and in general therapy should be continued. Slow or incomplete resolution of lymphocytosis does not appear to impact outcome as measured by PFS.[77] (See "Special Considerations for the Use of B-Cell Receptor Inhibitors (Ibrutinib and Idelalisib)," available online, in these guidelines, at NCCN.org [NHODG-E]).

Idelalisib (the isoform-selective oral inhibitor of PI3K-delta) in combination with rituximab is approved for the treatment of relapsed or refractory CLL. The efficacy of idelalisib monotherapy or in combination with rituximab was also shown in older patients (≥65 years) with previously untreated CLL and adverse risk factors.[87,88] In the preliminary analysis of a phase II study (n=37; median age, 70 years), idelalisib had substantial monotherapy activity resulting in an ORR of 81% (33% PR and 48% PR with lymphocytosis).[87] The most frequent grade 3 or higher treatment-related adverse events were rash (3%), diarrhea (3%), pneumonia (5%), transaminase elevation (8%), anemia (5%), and neutropenia (20%). In another phase II study (n = 64; median age, 71 years), the combination of idelalisib and rituximab induced an ORR in 97% of patients (78% PR and 19% CR).[88] Diarrhea/colitis (42%), pneumonia (19%), rash (13%), dehydration (8%), dyspnea (5%), and respiratory failure (5%) were the most frequent grade 3 or higher treatment-related adverse events. Similar early lymphocytosis as described with ibrutinib can occur with idelalisib and should be managed similarly.[76,89] (See "Special Considerations for the Use of B-Cell Receptor Inhibitors (Ibrutinib and Idelalisib)," available online, in these guidelines, at NCCN.org [NHODG-E])

Relapsed or Refractory Disease

The current standards of care for relapsed or refractory CLL are ibrutinib monotherapy and idelalisib plus rituximab.

Ibrutinib showed remarkable monotherapy activity with favorable toxicity profile in patients with relapsed/refractory B-cell malignancies.[90] The safety and efficacy of ibrutinib in relapsed or refractory CLL/SLL was first evaluated in a phase Ib/II study (n=85; 51 patients received 420 mg and 34 patients received 840 mg).[75] Most patients were considered to have high-risk features (advanced-stage disease, del(17p), and del(11q) were present in 65%, 33%, and 36% of patients, respectively). The ORR was the same (71%) in the 2 dose groups. Among the subgroup of 28 patients with del(17p), the ORR was 68% (CR in 3.5%). PR with lymphocytosis was seen in 20% and 15% of patients in the 2 dose groups (420 and 840 mg, respectively). The estimated PFS and OS at 26 months were 75% and 83%, respectively. The most common grade 3 or 4 adverse events included neutropenia (15%), pneumonia (12%), sinusitis (5%), and hypertension (5%).

In the subsequent phase III randomized study (RESONATE), 391 patients with previously treated CLL were randomized to monotherapy with ibrutinib (420 mg once daily) or ofatumumab.[91] Most patients had advanced-stage disease and high-risk features, including del(17p), del(11q), or elevated beta-2 microglobulin level (>3.5 mg/L). At a median follow-up of 9.4 months, ibrutinib significantly prolonged PFS

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(median not reached vs 8.1 months for ofatumumab) and OS (hazard ratio for death in the ibrutinib group was 0.43; $P=.005$; 57% reduction in the risk of death). Among patients with del(17p), median PFS was not reached with ibrutinib, compared with a median PFS of 5.8 months with ofatumumab. At 12 months, the OS rate was 91% and 81%, respectively, for ibrutinib and ofatumumab.[91] The ORR was also significantly higher with ibrutinib (42% vs 4%; $P<.001$). The most frequent nonhematologic adverse events were mild (grade 1–2) diarrhea, fatigue, pyrexia, and nausea in the ibrutinib group and fatigue, infusion-related reactions, and cough in the ofatumumab group. The updated results of this study also confirmed that ibrutinib significantly improved PFS, OS, and ORR compared with ofatumumab in patients with CLL/SLL who had received at least one prior therapy.[92] At a median follow-up of 16 months, ibrutinib showed significantly better ORR (90% vs 25%; $P<.0001$), median PFS (not reached vs 8.1 months for ofatumumab; $P<.0001$), and OS rates (18-month OS, 85% vs 78%, respectively). The results of the phase II study, RESONATE-17, further confirmed the efficacy of ibrutinib in patients with relapsed or refractory CLL with del(17p).[93] At a median follow-up of 13 months, the ORR and PFS rate were 82.6% and 79.3%, respectively.

Ibrutinib was approved by the FDA for the treatment of patients with CLL who received at least one previous therapy and for first-line therapy in patients with del(17p) CLL.

Idelalisib, the isoform-selective oral inhibitor of PI3K-delta, demonstrated promising clinical activity in phase I–II studies in patients with relapsed/refractory CLL, both as monotherapy and in combination with rituximab.[76,89] In a multicenter phase III randomized study, 220 patients with relapsed CLL were randomized to receive rituximab with either idelalisib (150 mg) or placebo.[76] Most of the patients (78%) were aged 65 years or older, 40% had moderate renal dysfunction (CrCl, <60 mL/min), 35% had poor bone marrow function (grade 3 or higher cytopenias), and 85% had a CIRS score greater than 6. At the first planned interim analysis, the study was stopped early due to the overwhelming efficacy of idelalisib plus rituximab.[76] At 24 weeks, the PFS rates were 93% and 46% in the idelalisib group and placebo group, respectively. Among patients with relapsed CLL with coexisting conditions, idelalisib

plus rituximab significantly improved ORR (81% vs 13%; $P<.001$), PFS (not reached in the idelalisib group vs 5.5 months in the placebo group), and OS at 12 months (92% vs 80%; $P=.02$), compared with rituximab plus placebo. Grade 3 or 4 adverse events (pneumonia, pyrexia, and febrile neutropenia) were reported in 40% of patients in the idelalisib group and 35% in the placebo group.

The second interim analysis of this study confirmed the superior safety and efficacy of idelalisib plus rituximab in terms of ORR, PFS, and OS.[94] Idelalisib plus rituximab also retained efficacy in patients with high-risk features such as del(17p) or TP53 mutations, unmutated IGHV, ZAP-70 and CD38 expression, and beta-2 microglobulin (>4 mg/L).[95] Idelalisib in combination with rituximab was recently approved for the treatment of relapsed CLL in patients for whom rituximab monotherapy would be considered inappropriate due to the presence of other comorbidities (reduced renal function as measured by CrCl <60 mL/min, or NCI CTCAE grade ≥3 neutropenia or thrombocytopenia resulting from myelotoxic effects of prior therapy with cytotoxic agents).

Ofatumumab is a fully human CD20 monoclonal antibody with activity in patients with CLL refractory to fludarabine and alemtuzumab or in patients for whom alemtuzumab is contraindicated due to bulky lymphadenopathy.[96] In the final analysis from the pivotal international clinical trial, which included data from 206 patients with either fludarabine- and alemtuzumab-refractory (FA-ref; n=95) CLL or fludarabine-refractory CLL with bulky lymphadenopathy (BF-ref; n=111), ofatumumab therapy resulted in an ORR of 51% in the FA-ref and 44% in the BF-ref patients.[97] The median PFS was 5.5 months for both groups, and the median OS was 14 and 17 months for the FA-ref and the BF-ref groups, respectively. The most common grade 3 or higher adverse events were infections (24%) and neutropenia (12%). An ad hoc retrospective analysis of patients with FA-ref CLL (n=96) and BF-ref CLL (n=111) showed that ofatumumab was also effective and well tolerated in patients with FA-ref CLL and previous rituximab exposure.[98] The ORRs were 43%, 44%, and 53%, respectively, for CLL with previous rituximab exposure, rituximab-refractory CLL, and rituximab-naive CLL. The median PFS times were 5.3, 5.5, and 5.6 months, respectively, and median

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OS times were 15.5, 15.5, and 20.2 months, respectively. Ofatumumab is approved for the treatment of patients with CLL refractory to fludarabine and alemtuzumab.

Obinutuzumab has monotherapy activity in patients with heavily pretreated relapsed/refractory CLL. In a phase II study of 20 patients (GAUGIN study), obinutuzumab at a fixed dose of 1000 mg resulted in a best ORR of 30%; median PFS and duration of response were 10.7 and 8.9 months, respectively.[99] A subset analysis of the CLL11 study showed that the combination of obinutuzumab plus chlorambucil was also active in patients with CLL refractory to prior treatment with chlorambucil.[100] Among the 30 patients who crossed over to obinutuzumab plus chlorambucil, clinical response was seen in 87% (77% PR, 7% CR, and 3% incomplete CR). The median PFS from start of crossover treatment was 17.2 months.

Allogeneic hematopoietic stem cell transplant (HSCT) was evaluated to improve the prognosis in patients with advanced disease and those with poor-risk features.[101–107] Available evidence from nonrandomized clinical studies suggest that allogeneic HSCT may be an effective treatment option for patients with disease refractory to chemoimmunotherapy or who develop recurrence within 12 months after treatment with purine analogs.[108]

Assessment of Functional Status and Comorbidity

CLL is diagnosed mainly in older adults, with a median age of 72 years at diagnosis. Approximately 70% of patients are diagnosed at age 65 years or older, and 40% of patients are diagnosed at age 75 years or older.[109] Comorbidities are frequently present in older patients. In addition, organ function and bone marrow reserve also decline with advancing age.

Although chemoimmunotherapy is now considered the standard of care for younger or fit older patients, it is often not well tolerated in older patients due to decline in organ function, reduced bone marrow reserve, and/or the presence of comorbidities.[110] In the first phase III randomized study (CLL5) that evaluated first-line chlorambucil versus fludarabine in a cohort of older patients (≥65 years) with untreated CLL, 65% of patients presented with at least one comorbidity, and approximately a third

of patients had 2 or more comorbidities at the time of enrollment.[111] In this trial, the presence of multiple comorbidities was a negative prognostic factor independent of disease stage or age. In multivariate analysis, elevated serum beta-2 microglobulin and the presence of 2 or more comorbidities were significant independent predictors of shorter PFS and OS.[111] Several retrospective studies also reported on the negative impact of comorbidities on patient outcomes in CLL.[112–114] The most common comorbidities reported include hypertension (19%–53%), coronary artery disease (7%–24%), hyperlipidemia or lipometabolic disease (16%–38%), and diabetes mellitus (10%–21%).[112–114]

These findings underscore the need to assess comorbidities, in addition to patient age and performance status, before treatment selection. The tolerability of a treatment regimen relative to a patient's physical fitness is an important consideration in the management of CLL. The CIRS, Charlson comorbidity index, and NCI comorbidity index are some of the scoring systems that can be used to assess comorbidities in patients with CLL. CIRS in combination with CrCl was used by the GCLLSG to assess the overall fitness of patients enrolled in clinical trials.[47,115]

NCCN Recommendations

Localized SLL (Ann Arbor Stage I)
Locoregional radiation therapy (RT) is an appropriate induction therapy for patients with symptomatic localized disease. In rare patients, RT may be contraindicated or may be a suboptimal therapy due to the presence of comorbidities or the potential for long-term toxicity. Patients with localized SLL that has progressed after initial RT should be treated as described subsequently for patients with SLL (Ann Arbor stage II–IV).

SLL (Ann Arbor Stages II–IV) or CLL (Rai Stages 0–IV)
Early-stage disease in some patients may have an indolent course and in others may progress rapidly to advanced disease requiring immediate treatment. A "watch and wait" approach is often appropriate for patients with early-stage, low-risk disease (Rai stage 0; Binet A) in the absence of disease symptoms.

Patients with Binet B or intermediate-risk disease (Rai stage I or II) may benefit from therapy if

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they show evidence of progressive disease or become symptomatic.[3] Patients with advanced-stage or high-risk CLL (Binet C; Rai stage III–IV) with progressive cytopenia require immediate treatment. Selected patients with mild, stable cytopenia may continue to be observed.

Absolute lymphocyte count alone is not an indication for treatment unless it is greater than 200 to 300 x 10^9/L or symptoms related to leukostasis occur. Standard indications for initiating treatment include the following[3]: significant disease related constitutional symptoms including severe fatigue, weight loss, night sweats and fever without infection; threatened end-organ function; progressive bulky disease (enlarged spleen or lymph nodes); progressive anemia or thrombocytopenia; or autoimmune anemia/thrombocytopenia unresponsive to corticosteroids. Asymptomatic patients should be observed until such indications (as mentioned previously) become apparent.

Given the incurability of the disease, the NCCN Guidelines recommend enrollment in clinical trials, when locally available, as the preferred option for all patients with indications for treatment. In the absence of suitable clinical trials, the treatment recommendations included in the NCCN Guidelines are based on patient's age or functional status (comorbidity index/performance status) and the presence or absence of del(17p) and/or del(11q).

Management of Frail Patients With Significant Comorbidity

Obinutuzumab plus chlorambucil (category 1),[81] ofatumumab plus chlorambucil,[83] and rituximab plus chlorambucil[116,117] are the preferred treatment options for frail patients with significant comorbidities that preclude treatment with purine analogs. Obinutuzumab monotherapy is included as an alternative option with a category 2B recommendation.[82] See "Suggested Treatment Regimens: Frail Patient, Significant Comorbidity (not able to tolerate purine analogs)" (CSLL-D, 1 of 7; page 339) for a list of other suggested regimens.

Management of Patients With Adequate Functional Status

Patients with adequate functional status can be treated with more active or intensive therapies and should be evaluated for cytogenetic abnormalities by FISH. Patient age and the presence or absence of del(17p) and/or del(11q) should then help to direct treatment options, as shown in later sections.

CLL Without del(17p) or del(11q)

For patients aged 70 years or older and younger patients with significant comorbidities, obinutuzumab plus chlorambucil (category 1)[81] is the preferred first-line regimen, followed by ofatumumab plus chlorambucil.[83] Obinutuzumab monotherapy is included as an alternative option with a category 2B recommendation.[82] In patients younger than 70 years without significant comorbidities, fludarabine-based chemoimmunotherapy has emerged as the standard of care.[47,56,118] Bendamustine plus rituximab is a reasonable alternative for patients aged 70 years or older who are otherwise eligible for chemoimmunotherapy.[118,119]

Based on the recent FDA approvals, ibrutinib (category 1)[91] and idelalisib with or without rituximab[76,120] are included as preferred options for patients with relapsed or refractory disease, regardless of their age and comorbidities. Monotherapy with ofatumumab or obinutuzumab are included as alternative options. Allogeneic HSCT can be considered for select patients (without significant comorbidities) after reinduction of remission.

See "Suggested Treatment Regimens: CLL Without del(11q) or del(17p)" (CSLL-D, 1 and 2 of 7; pages 339 and 340) for a list of other suggested regimens

CLL With del(17p)

Outcomes remain poor with currently available chemoimmunotherapy regimens. Enrollment in an appropriate clinical trial is recommended for patients with del(17p). In the absence of appropriate clinical trials in the patient's local area, based on the recent FDA approval, ibrutinib is included as an option for first-line therapy.

Patients with response to first-line therapy should be considered for allogeneic HSCT, if they are eligible. However, the role of allogeneic HSCT in the up-front setting is evolving with the introduction of new therapies such as ibrutinib. Patients with a response after allogeneic HSCT can either be observed or enrolled in clinical trials. Patients with no response to first-line therapy, patients who respond to first-line therapy but are not eligible for allogenic HSCT, and patients with no response to allogenic HSCT should be enrolled in clinical trials

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or be treated with second-line therapy for relapsed or refractory disease.

Ibrutinib and idelalisib with or without rituximab are the preferred options for relapsed or refractory disease.[84–86,91] The efficacy of ibrutinib in patients with relapsed or refractory CLL with del(17p) exceeds the results of alternative regimens in the upfront setting and should be considered as the best choice in the absence of a contraindication to give this treatment.

See "Suggested Treatment Regimens: CLL with del(17p)" (CSLL-D, 3 of 7; page 341) for a list of other suggested regimens.

CLL With del(11q)

Outcomes are more favorable for patients treated with alkylating agent–based chemoimmunotherapy regimens. For patients younger than 70 years without significant comorbidities, first-line treatment options include FCR, bendamustine with or without rituximab, or PCR. For patients aged 70 years or older and younger patients with comorbidities, preferred first-line treatment options include obinutuzumab plus chlorambucil (category 1),[81] followed by ofatumumab plus chlorambucil.[83]

Patients who experienced CR to first-line therapy can either be observed until disease progression or enrolled in clinical trials. Patients with PR to first-line therapy should be considered for allogeneic HSCT, if they are eligible. However, the role of allogeneic HSCT is evolving with the introduction of new targeted therapies. After transplantation, treatment options are similar to those described for patients with del(17p).

Patients with no response to first-line therapy and patients with PR to first-line therapy but who are not eligible for allogenic HSCT should be enrolled in clinical trials or can be treated with second-line therapy for relapsed or refractory disease. Ibrutinib and idelalisib with or without rituximab are the preferred options for relapsed or refractory disease.

See "Suggested Treatment Regimens: CLL with del(11q)" (CSLL-D, 4 and 5 of 7; pages 342 and 343) for a list of other suggested regimens based on the patient's age and the presence or absence of significant comorbidities.

Histologic Transformation

Approximately 2% to 10% of patients with CLL will develop Richter's transformation (histologic transformation to diffuse large B-cell lymphoma or Hodgkin lymphoma) during the course of their disease and treatment.[121–123] The incidence of histologic transformation increases with the number of prior regimens. Recent reports identified inactivation of NOTCH1 and disruption of TP53 and CDKN2A/B as possible genetic pathways involved in the pathogenesis of Richter's transformation.[124,125]

Patients with Richter's transformation should be treated with chemoimmunotherapy regimens initially developed for diffuse large B-cell lymphoma.[126,127] OFAR and hyper-CVAD with rituximab were also used for the treatment of patients with Richter's transformation.[128–130] Allogeneic HSCT can also be considered after a response to initial therapy in patients with Richter's transformation. In a nonrandomized comparative analysis, the estimated cumulative 3-year survival rate was significantly higher (75%) for patients who underwent allogeneic HSCT after achieving CR or PR to initial therapy compared with those who responded to initial therapy but did not undergo allogeneic HSCT, or who underwent allogeneic HSCT for relapsed or refractory Richter's transformation (75% vs 27% and 21%, respectively; P=.019).[126] High-dose therapy/autologous stem cell rescue may also be an appropriate therapy for patients with Richter's transformation who have a response to initial therapy but are not a candidate for allogeneic HSCT due to age, comorbidities, or lack of a suitable donor.[131] Patients with Hodgkin histology should receive a standard regimen used for the treatment of Hodgkin lymphoma.

Supportive Care for Patients With CLL

Management of disease-specific complications is an integral part of the management of patients with CLL/SLL. See "Supportive Care for Patients With CLL" (CSLL-C; pages 337 and 338) for specific recommendations.

Summary

CLL is diagnosed mainly in older adults, who often present with multiple comorbidities. Cytogenetic abnormalities identified in most patients also have an impact on the clinical outcome. In addition to the disease stage and patient age, treatment options for patients with symptomatic disease should

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be based the presence or absence of comorbid conditions and/or poor prognostic features. Obinutuzumab plus chlorambucil is the new standard of care for both elderly patients and patients with comorbid conditions, lacking del(17p). Ibrutinib or idelalisib with rituximab are effective treatment options for patients with relapsed or refractory CLL. In addition, ibrutinib monotherapy is also an option for first-line therapy in patients with del(17p). Supportive care for the management of disease-specific complications should also be an integral part in the management of patients with CLL.

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The NCCN Guidelines staff have disclosed that they have no conflicts of interest.