Treatment of Chronic Lymphocytic Leukemia and Small Lymphocytic Lymphoma
Chronic Lymphocytic Leukemia – (CLL)

- Common hematologic malignancy, particularly in western countries
- Accounts for 1/3 of leukemias worldwide.
- Predominantly affects older adults; median age at diagnosis ~70 years.
- Usually asymptomatic at diagnosis; found on routine CBC.
- Elevated WBC and ALC.
- Immunophenotype: CD5+, CD19+, CD20+ (usually dim), CD23+
- In the US, CLL is staged using the Rai System.
- Outside the US, the Binet System is often used.
Diagnosis – CLL/SLL

NCCN Guidelines Version 2.2018
Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

DIAGNOSIS

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.
- Flow cytometry of blood adequate for diagnosis of CLL/SLL (biopsy generally not required).
- CLL diagnosis requires presence of monoclonal B lymphocytes ≥5 x 10⁹/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: κ/λ, CD19, CD20, CD5, CD23, CD10; if flow is used to establish diagnosis, also include cytoplasmic cyclin D1 or FISH for t(11;14); t(11q;14). CD200 may be useful to distinguish from MCL.
- CLL/SLL diagnosis requires presence of lymphadenopathy and/or splenomegaly with B lymphocytes ≤5 x 10⁹/L in peripheral blood.
- CLL/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. Bone marrow aspirate with biopsy if consult material is nondiagnostic. 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: CD3, CD5, CD10, CD20, CD23, cyclin D1. LEF1 may be useful to distinguish from MCL.
- Absolute monoclonal B lymphocyte count ≤5000/μL

INFORMATIVE FOR PROGNOSTIC AND/OR THERAPY DETERMINATION:
- FISH to detect: +12; del(11q); del(13q); del(17p)
- TP53 sequencing
- Cpg-stimulated metaphase karyotype for complex karyotype
- Molecular analysis to detect: IGHV mutation status

CLL = chronic lymphocytic leukemia; SLL = small lymphocytic lymphoma. Cases diagnosed as B-cell prolymphocytic leukemia (B-PLL) are excluded from this guideline.

Typical immunophenotype: CD5+, CD23+, CD24+, 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).

Table 1. Diagnosis of CLL

<table>
<thead>
<tr>
<th>Clonal expansion of abnormal B lymphocytes in PB</th>
</tr>
</thead>
<tbody>
<tr>
<td>At least 5 x 10⁹ B lymphocytes/L (5000/μL)</td>
</tr>
<tr>
<td>Lymphoid cells ≤ 55% atypical/immature</td>
</tr>
<tr>
<td>Low density of surface Ig (IgM or IgD) with κ or λ light chains</td>
</tr>
<tr>
<td>B-cell surface antigens (CD19, CD20&lt;sub&gt;dim&lt;/sub&gt;, CD23)</td>
</tr>
<tr>
<td>CD5 surface antigen</td>
</tr>
</tbody>
</table>
Chronic Lymphocytic Leukemia - 1
Chronic Lymphocytic Leukemia: Thrombocytopenia - 3.
Chronic Lymphocytic Leukemia - 5
“Prolymphocyte with two prominent nucleoli (clear spaces) in the peripheral blood of a patient with the prolymphocytic variant of chronic lymphocytic leukemia (CLL).” - ASH Image Bank
Rai Staging

- Stage 0: Lymphocytosis: ALC > 5,000/μL
- Stage 1: Enlargement of lymph nodes
- Stage 2: Enlargement of spleen or liver
- Stage 3: Anemia
- Stage 4: Thrombocytopenia
Binet Staging

• Stage A:
  – **Fewer than** three areas of enlarged lymphoid tissue.
  – No anemia
  – No thrombocytopenia
  – Lymphadenopathy in the neck, axillary, inguinal regions, or splenic involvement

• Stage B:
  – **Three or more** areas of enlarged lymphoid tissue
  – No anemia
  – No thrombocytopenia

• Stage C:
  – Anemia and/or thrombocytopenia, regardless of lymphadenopathy or splenomegaly
Prognosis

Several factors aid in predicting prognosis:

• Clinical stage
• Tumor burden
• Lymphocyte doubling time
• Morphologic features
  – Presence of prolymphocytes
• Chromosomal abnormalities
  – del(13q): favorable prognosis
  – del(17p): poor prognosis (TP53 deletion)
• Immunophenotypic markers
  – Elevated CD38 and ZAP-70 have been associated with shorter survival
Prognostic Significance of Chromosomal Abnormalities

## Immunophenotypic Differentiation of CLL from Other B-lineage Lymphomas

### Table 2. Immunophenotypic and genetic features of other B-cell lymphomas that may be confused with CLL

<table>
<thead>
<tr>
<th>Neoplasm</th>
<th>Slg</th>
<th>clg</th>
<th>CD5</th>
<th>CD10</th>
<th>CD23</th>
<th>CD43</th>
<th>Cyclin D1</th>
<th>Bcl-6 protein*</th>
<th>Genetic abnormality (%)</th>
<th>IgVH genes</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLL</td>
<td>+</td>
<td>-/+</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>del13q (50); del 11q (20); trisomy 12 (20); del 17p (10)</td>
<td>50% unmutated</td>
</tr>
<tr>
<td>LPL</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-/+</td>
<td>-</td>
<td>-</td>
<td>t(9;14)-PAX5R</td>
<td>Mutated</td>
</tr>
<tr>
<td>MCL</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>t(11;14)-BCL1R</td>
<td>Unmutated (rarely mutated)</td>
</tr>
<tr>
<td>FL</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-/+</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>t(14;18)-BCL2R</td>
<td>Mutated, ongoing</td>
</tr>
<tr>
<td>Extranodal and nodal MZL</td>
<td>+</td>
<td>-/+</td>
<td>-</td>
<td>-</td>
<td>-/+</td>
<td>-/+</td>
<td>-</td>
<td>-</td>
<td>trisomy 3; t(11;18)-API2/MLT; t(1;14)-BCL10R</td>
<td>Mutated, ongoing</td>
</tr>
<tr>
<td>Splenic MZL</td>
<td>+</td>
<td>-/+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>del 7q21-32 (40)</td>
<td>50% mutated</td>
</tr>
</tbody>
</table>

LPL indicates lymphoplasmacytic lymphoma; MCL, mantle cell lymphoma; FL, follicle center lymphoma; MZL, marginal zone lymphoma; +, more than 90% positive; -/+ less than 50% positive; and -, less than 10% positive.

*Residual GC may be + in MZL, MCL.
Prognostic Significance of CD38 Expression and Ig V Gene Mutation Status

**Figure 2.** Elevated expression levels of CD38 and ZAP-70 have been associated with shorter survival in patients with chronic lymphocytic leukemia. Adapted from Damle RN et al. *Blood.* 1999;94(6):1840-1847.7

**Figure 3.** The mutational status of the *IGHV* gene has prognostic significance in chronic lymphocytic leukemia. *IGHV*, immunoglobulin heavy-chain variable. Adapted from Hamblin TJ et al. *Blood.* 1999;94(6):1848-1854.8
Gene expression profiling of Ig-mutated and -unmutated CLL

Adrian Wiestner et al., Blood 2003;101:4944-4951

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Diagnostic Workup

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Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

WORKUP

ESSENTIAL:
- History and physical exam including measurement of size of liver and spleen
- Performance status
- B symptoms
- CBC with differential
- Comprehensive metabolic panel

USEFUL UNDER CERTAIN CIRCUMSTANCES:
- Quantitative immunoglobulins
- Reticulocyte count, haptoglobin, and direct Coombs' test
- Chest/abdominal/pelvic CT with contrast of diagnostic quality, if clinically indicated\(^7\)
- Beta-2-microglobulin
- LDH
- Uric acid
- Unilateral bone marrow aspirate + biopsy at initiation of therapy
- Hepatitis B testing\(^9\) if treatment contemplated
- MUGA scan/echocardiogram if anthracycline- or anthracedione-based regimen is indicated
- Pregnancy testing in women of child-bearing age if systemic therapy or RT planned
- Discussion of fertility issues and sperm banking
- PET/CT scan to direct nodal biopsy, if histologic transformation is suspected. See HT-1.

\(^1\)Outside clinical trials, CT scans are not necessary for diagnosis, surveillance, routine monitoring of treatment response, or progression. May be warranted for symptoms or to evaluate bulky disease.
\(^9\)Hepatitis B testing is indicated because of the risk of reactivation during treatment (eg, immunotherapy, chemoimmunotherapy, chemotherapy, targeted therapy). 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.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.
Treatment (1)

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Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

PRESENTATION
- SLL/Localized
  (Lugano Stage I)
- Locoregional RT
  (24–30 Gy)
  (if indicated)
- Observe
  Evaluate for indications for treatment:
  - Eligible for clinical trial
  - 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
- No indication
- SLL
- CLL
  (Rai Stages I
  0-IV)
  or
  SLL
  (Lugano Stage II-IV)
- CLL
  (Rai Low (0)
  and
  Intermediate (I-II) risk)
- CLL
  (Rai High
  (III-IV) risk)
- Progressive cytopenia
- Histologic transformation
  or
  Histologic progression of CLL
- See HT-1

Consider prophylaxis for tumor lysis syndrome (See CSLL-C)
See monoclonal antibody and viral reactivation (CSLL-C)

CLL/PLL Without Deletion of 17p/TP53 Mutation (See CSLL-4)
- Re-evaluate
  - FISH
  - TP53 mutation status
  - Karyotype
  - Imaging as appropriate

CLL/PLL With Deletion of 17p/TP53 Mutation
(See CSLL-6)

Note: All recommendations are category 2A unless otherwise indicated.
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CSLL-3
Treatment (2)

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Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

CLL/SLL WITHOUT DELETION OF 17p/TP53 MUTATION\textsuperscript{h,k,l}

FIRST-LINE THERAPY\textsuperscript{h}

Frail patients with significant comorbidity\textsuperscript{p} (not able to tolerate purine analogs) → See Suggested Regimens (CSLL-D 1 of 5)

Relapsed or refractory CLL/SLL with indication for treatment (See CSLL-3)

RELAPSED/REFRACTORY THERAPY\textsuperscript{h}

\begin{itemize}
  \item Re-evaluate\textsuperscript{0}
    \begin{itemize}
      \item FISH
      \item TP53 mutation status
      \item Karyotype
      \item If del(17p), see CSLL-6
    \end{itemize}
  \item If histologic transformation or histologic progression of CLL, see HT-1.
\end{itemize}

- CLL/SLL without del(17p)/TP53 mutation\textsuperscript{h,k,l}

  - Age ≥65 y and younger patients with significant comorbidities\textsuperscript{p} → See CSLL-5

  - Age <65 y without significant comorbidities\textsuperscript{p} → See CSLL-5

Consider prophylaxis for tumor lysis syndrome (See CSLL-C)

See monoclonal antibody and viral reactivation (CSLL-C)

\textsuperscript{h}See Supportive Care for Patients with CLL/SLL (CSLL-C).

\textsuperscript{p}Absolute lymphocyte count alone is not an indication for treatment unless above 200–300 x 10\textsuperscript{9}/L or symptoms related to leukostasis.

\textsuperscript{k}Given incurability with conventional therapy, consider including clinical trial as first-line therapy.

\textsuperscript{l}Re-evaluation of FISH [t(11;14); t(11q;v); +12; del(11q); del(13q); del(17p)] and TP53 mutation status is necessary prior to initiation of treatment.


\textbf{Note:} All recommendations are category 2A unless otherwise indicated. Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.
Treatment: Frontline

• First-line regimens depend on patient age, general health, disease-related factors, and patient’s individual treatment goals.

• Older patients with comorbidities:
  – Chlorambucil monotherapy, rituximab monotherapy, or combination of chlorambucil and rituximab (a regimen used primarily outside the US).

• Younger patients without comorbidities:
  – Combination chemoimmunotherapy regimens, such as bendamustine and rituximab, or fludarabine, cyclophosphamide, and rituximab (FCR) have become standard of care.
Frontline Treatment: German CLL Study Group

Figure 1. German CLL first-line treatment guidelines

- Asymptomatic
  - ALL
    - W & W
      - Without del(17p) or TP53mut
        - <65 years of age
          - FCR
          - CD20
          - CD20 or Alemtuzumab
          - SDPR
          - W & W
        - >65 years of age
          - BR
          - BR or CD20
          - BR or CD20 or CD20 or CD20
          - SDPR
          - W & W
          - Second-line therapy
      - With del(17p) or TP53mut
        - BR or CD20 or CD20 or CD20 or CD20
        - SDPR
        - W & W
        - Second-line therapy
  - Symptomatic
    - Unfit (slow go)
      - Without del(17p) or TP53mut
        - BR or CD20 or CD20 or CD20 or CD20
        - SDPR
        - W & W
        - Second-line therapy
    - Frail (no go)
      - BR or CD20 or CD20 or CD20 or CD20
      - SDPR
      - W & W
      - Second-line therapy

Legend:
- B-Ofa = bendamustine, ofatumumab
- BR = bendamustine, rituximab
- BSC = best supportive care
- CLL = chronic lymphocytic leukemia
- CR = complete response
- del(17p) = deletion 17p
- FCR = fludarabine, cyclophosphamide, rituximab
- G-Cib = oblimersen, chlorambucil, idelalisib, rituximab, ofatumumab, chlorambucil
- PD = progressive disease
- PR = partial response
- R-Cib = rituximab, chlorambucil, TP53mut = TP53 mutation
- W & W = watch and wait
Ibrutinib

- Approved by the FDA in 2016 for the frontline setting.
- Useful for elderly and high-risk patients (e.g., TP53 deletion)
- Acts by interfering with key signaling events that are activated in CLL cells within the microenvironment of secondary lymphoid tissues.
- Administered orally.
- Works by a redistribution of the CLL cells out of the lymphoid tissues into the peripheral blood, where they are cleared and then lead to remission.
Persistent Lymphocytosis with Ibrutinib

Figure 7. Cumulative best responses seen with single-agent ibrutinib after 3 years of follow-up among patients with chronic lymphocytic leukemia (symptomatic treatment-naive or relapsed/refractory) or small lymphocytic lymphoma. CR, complete response; PR, partial response; PR-L, partial response with lymphocytosis. Adapted from Byrd JC et al. Blood. 2015;125(16):2497-2506.
Figure 8. PFS in the phase 3 HELIOS trial, which evaluatedibrutinib plus BR vs placebo plus BR in patients with relapsed/refractory chronic lymphocytic leukemia or small lymphocytic lymphoma. BR, bendamustine and rituximab; HELIOS, Ibrutinib Combined With Bendamustine and Rituximab Compared With Placebo, Bendamustine, and Rituximab for Previously Treated Chronic Lymphocytic Leukaemia or Small Lymphocytic Lymphoma; ITT, intent-to-treat; PFS, progression-free survival. Adapted from Chanan-Khan A et al. Lancet Oncol. 2016;17(2):200-211.12
Idelalisib

• Selective inhibitor of PI3 kinase delta that is FDA-approved for relapsed CLL in combination with rituximab.
• Dosed orally, twice daily.
• Safety profile is different than of idelalisib in that adverse advents are much higher and more sever.
• At this time should only be used in the salvage setting.
Venetoclax

• Orally administered inhibitor of BCL-2.
• BCL-2 is an antiapoptotic protein crucial to the survival of CLL cells.
• Indicated for patients with 17p deletion after 1 or more previous therapies.
• Approved by the FDA in April 2016.
• Adverse events include tumor lysis syndrome that can be life-threatening. Patients must be hospitalized when drug is administered.
• ORR was 79% in recent trial with 20% CR.
Potential anti-CD20 mAb Effector Mechanisms

Complement dependent cytotoxicity

Homotypic adhesion and lysosomal-dependent non-apoptotic cell death

Fc-FcγR dependent mechanisms

Malignant B-cell

EFFECTOR CELL

DENDRITIC CELL

ACTIVATED T-CELLS

Adaptive cellular immunity

Waleed Alduaij, and Tim M. Illidge Blood 2011;117:2993-3001

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## Commercially Available anti-CD20 mAbs

### Table 2: Comparison of commercially available anti-CD20 antibodies

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Obinutuzumab</th>
<th>Rituximab</th>
<th>Ofatumumab</th>
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<tbody>
<tr>
<td>Trade name (EU)</td>
<td>Gazyvaro</td>
<td>MabThera</td>
<td>Arzerra</td>
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<tr>
<td>Manufacturer</td>
<td>Roche</td>
<td>Roche</td>
<td>GlaxoSmithKline</td>
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<tr>
<td>Antibody type</td>
<td>II</td>
<td>I</td>
<td>I</td>
</tr>
<tr>
<td>IgG subclass</td>
<td>IgG1</td>
<td>IgG1</td>
<td>IgG1</td>
</tr>
<tr>
<td>Structure</td>
<td>Humanized</td>
<td>Chimeric</td>
<td>Fully human</td>
</tr>
<tr>
<td>Binding to CD20 epitope</td>
<td>Large loop</td>
<td>Large loop</td>
<td>Large and small loop</td>
</tr>
<tr>
<td>Binding to lipid rafts</td>
<td>–</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>ADCC</td>
<td>+++</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>CDC</td>
<td>+</td>
<td>++</td>
<td>+++</td>
</tr>
<tr>
<td>Direct cell death induction</td>
<td>+++</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

**Abbreviations:** ADCC, antibody-dependent cellular cytotoxicity; CDC, complement-dependent cytotoxicity; Ig, immunoglobulin.
Ublituximab: anti-CD20 mAb

Anti-CD20 Monoclonal Antibody Ublituximab for B-Cell NHL/CLL

- **Induction**
  - **NHL**: Cycle 1, Weekly treatment days 1, 8, 15, 22
  - **CLL/SLL**: Cycles 1, 2, Weekly treatment days 1, 8, 15

- **Assessment**
  - If no PD continue

- **Maintenance**
  - Cycles 3, 4, 5: Patients without progression continue with monthly treatment at same dose

- **Assessment**
  - If no PD continue

- **Maintenance**
  - Cycles 6, 9, 12: Every 3 months at same dose thereafter for a maximum of 2 years

1 cycle = 28 days

http://doi.org/10.1111/bjh.14534
Ublituximab: anti-CD20 mAb

Anti-CD20 Monoclonal Antibody Ublituximab for B-Cell NHL/CLL

(A)

<table>
<thead>
<tr>
<th>Type</th>
<th>Pts (n)</th>
<th>CR n (%)</th>
<th>PR n (%)</th>
<th>ORR n (%)</th>
<th>SD n (%)</th>
<th>PD n (%)</th>
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<tbody>
<tr>
<td>CLL</td>
<td>6</td>
<td>-</td>
<td>3 (50)</td>
<td>3 (50)</td>
<td>3 (50)</td>
<td>-</td>
</tr>
<tr>
<td>FL</td>
<td>12</td>
<td>2 (17)</td>
<td>3 (25)</td>
<td>5 (42)</td>
<td>5 (42)</td>
<td>2 (17)</td>
</tr>
<tr>
<td>MZL</td>
<td>7</td>
<td>2 (29)</td>
<td>3 (43)</td>
<td>5 (71)</td>
<td>2 (29)</td>
<td>-</td>
</tr>
<tr>
<td>MCL</td>
<td>5</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>4 (80)</td>
<td>1 (20)</td>
</tr>
<tr>
<td>DLBCL</td>
<td>1</td>
<td>-</td>
<td>1 (100)</td>
<td>1 (100)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Total</td>
<td>31</td>
<td>4 (13)</td>
<td>10 (32)</td>
<td>14 (45)</td>
<td>14 (45)</td>
<td>3 (10)</td>
</tr>
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</table>

Overall response (% patients)

53%

50% PR
21% CR
32% PR
17% PR
13% CR
32% PR

(B)

% Change from baseline in nodal size

Rituximab-relapsed
Rituximab-refractory

Tumor type
Ublituximab: anti-CD20 mAb

Fig 2. Treatment Response. (A) Overall response by lymphoma subtype. (B) Individual patient best percentage change from baseline in nodal size. (C) Progression-free survival. aNHL, aggressive non-Hodgkin lymphoma; CI, confidence interval; CLL, chronic lymphocytic leukaemia; CR, complete response; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; iNHL, indolent non-Hodgkin lymphoma; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; ORR, overall response rate; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease.

Median PFS:
- All patients: 7.7 months (95% CI: 4.5–16.2 months)
- Rituximab-refractory: 4.7 months (95% CI: 1.9–6.2 months)
Autoimmune Complications in Patients with CLL

Figure 2. How I treat autoimmune hemolytic anemia in CLL.
Direct antiglobulin test in diagnosis of hemolytic anemia

* DAT TEST RESULT

IgG+ and C3-

IgG+ and C3+

IgG- and C3+

TYPE OF AIHA

Warm

Warm

Cold Agglutinin Disease

Paroxysmal Cold Hemoglobinuria

ANTIGEN INVOLVED

Rh ± drug

Glycophorin ± drug

I- or i- antigen

P-antigen

Glycophorin ± drug

CAUSES

Idiopathic; autoimmune disease; drug; lymphoma

Idiopathic; autoimmune disease; drug; lymphoma

IgM monoclonal gammopathy; Waldenström macroglobulinemia; Mycoplasma pneumonia;

Viral infection; lymphoma

Idiopathic; autoimmune disease; drug; lymphoma

Ronald S. Go et al. Blood 2017;129:2971-2979
Supportive Care for Patients with CLL

NCCN Guidelines Version 2.2018
Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

SUPPORTIVE CARE FOR PATIENTS WITH CLL/SLL

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)

Blood Product Support
• Transfuse according to institutional or published standards
• Irradiate all blood products to avoid transfusion-associated GVHD

Cancer Screening
• Standard screening guidelines should be closely followed for breast, cervical, colon, and prostate cancers

Non-Melanomatos Skin Cancer
• Patients with CLL/SLL have a higher risk of developing non-melanomatos skin cancers
• Risk factors include caucasians and a history of intensive sun exposure at a young age
• For patients at-risk, annual dermatologic skin screening is recommended

Rare Complications of Monoclonal Antibody Therapy
• Rare complications such as mucocutaneous reactions including paraneoplastic pemphigus, Steven-Johnson syndrome, lichenoid dermatitis, vesiculobullous dermatitis, and toxic epidermal necrolysis can occur. Consultation with a dermatologist is recommended for management of these complications. Re-challenge with the same monoclonal antibody in such settings is not recommended. It is unclear that re-challenge with alternative CD20 antibodies poses the same risk of recurrence.

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

Rituximab Rapid Infusion
• If no infusion reactions were experienced with prior cycle of rituximab, a rapid infusion over 90 minutes can be used.

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

- Many patients with CLL/SLL do not require treatment until they become symptomatic.
- Autoimmune complications can arise which include:
  - Autoimmune hemolytic (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)
- Variety of effective regimens are available:
  - FCR: fludarabine, cyclophosphamide, and rituximab
  - Bendamustine (usually with rituximab)
  - FR: fludarabine and rituximab
  - CVP: cyclophosphamide, vincristine, and prednisone (sometimes with rituximab, R-CVP)
  - CHOP: cyclophosphamide, doxorubicin, vincristine, and prednisone
  - Chlorambucil combined with prednisone, rituximab, obinutuzumab, or ofatumumab
  - PCR: pentostatin, cyclophosphamide, and rituximab
  - Alemtuzumab
  - Fludarabine
  - Ibrutinib

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