Treatment of Chronic Lymphocytic Leukemia and Small Lymphocytic Lymphoma
Chronic Lymphocytic Leukemia

- Relatively common hematologic malignancy.
- Accounts for 1/3 of all leukemias worldwide.
- Predominantly affects older adults—median age 70-72 years.
- Usually asymptomatic at diagnosis; found on routine CBC.
- Elevated WBC and ALC.
- Phenotype on flow cytometry: CD5+, CD23+, CD19+, CD20+.
- In the United States, CLL is staged using the Rai System.
- Outside United States, the Binet System is often used.
Rai Staging

- Stage 0: Lymphocytosis
- 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 and splenic involvement

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

• Stage C:
  – Patients have anemia and/or thrombocytopenia regardless of lymphadenopathy
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)
• Immunophenotypic markers
  – Elevated CD38 and ZAP-70 have been associated with shorter survival
“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
Prognostic Significance of Chromosomal Abnormalities

Prognostic Significance of Immunophenotypic Markers

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.

Treatment

• 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 the standard of care.
Ibrutinib

- Approved by the FDA in 2016 for the frontline setting.
- Useful for elderly and high-risk patients and can be used alone or with chlorambucil.
- Act 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 in the peripheral blood, where they are cleared and then lead to remission.
Single-Agent Ibrutinib

Figure 7. Cumulative best responses seen with single-agent ibritinib 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.
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.
Figure 8. PFS in the phase 3 HELIOS trial, which evaluated ibrutinib 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. 

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**ITT population**

Median follow-up: 17.02 months

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<td>Median PFS (months)</td>
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Venetoclax

- Orally administered inhibitor of BCL-2.

- BCL-2 is an antiapoptotic protein crucial to the survival of CLL cells.

- Used for patients with the 17p deletion and have been on 1 previous treatment.

- Approved by the FDA in April 2016.

- Adverse events include tumor lysis syndrome. Patients must be hospitalized when drug is administered.

- ORR was 79% in recent trial and 20% CR.
Summary

- Many patients do not require treatment until they become symptomatic.
- Variety of effective regimens are available for treatment:
  - FCR: fludarabine (Fludara), cyclophosphamide (Cytoxan), and rituximab
  - Bendamustine (sometimes with rituximab)
  - FR: fludarabine and rituximab
  - CVP: cyclophosphamide, vincristine, and prednisone (sometimes with rituximab, R-CVP)
  - CHOP: cyclophosphamide, doxorubicin, vincristine (Oncovin), and prednisone
  - Chlorambucil combined with prednisone, rituximab, obinutuzumab, or ofatumumab
  - PCR: pentostatin (Nipent), cyclophosphamide, and rituximab
  - Alemtuzumab (Campath)
  - Fludarabine (alone)
  - Ibrutinib (alone)
References

• Clinical Advances in Hematology & Oncology, Volume 14, Issue 5, Supplement 8, May 2016


• NCCN Guidelines:
  https://www.nccn.org/professionals/physician_gls/f_guidelines.asp#site