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Smart Patients Get Smart Care™

Just diagnosed: What do I need to know?

April 28, 2020

Housekeeping Notes

- Please direct your questions to CLL Society faculty or staff using the Q&A function (located at the bottom of your screen) at any time throughout the presentation. The audience is muted.
- Questions can only be seen by staff and speakers. We will do our best to answer as many questions as possible.
- You will receive a short email survey after the webinar. Your response will help CLL Society plan future webinars.
- The webinar is being recorded and all recorded webinars and the presentation slides will be available on our website via the Support Groups/Education page on cllsociety.org.

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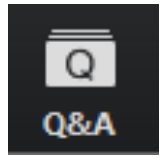

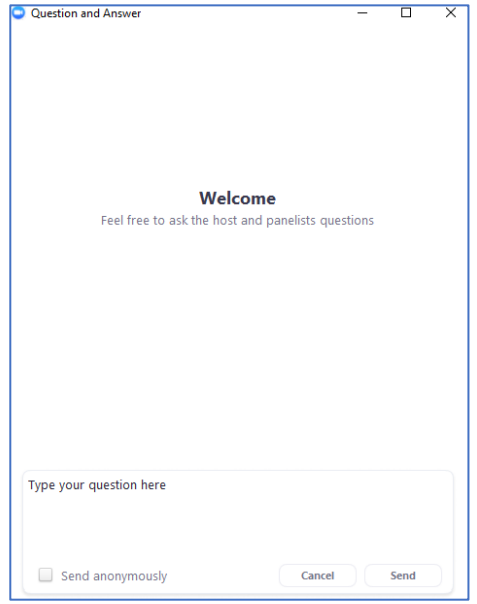

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Speakers

Welcome: Patty Koffman, Co-founder and Communications Director, CLL Society

Moderator: Brian Koffman, MDCM (retired), DCFP, FCFP, DABFP, MSEd

Executive Vice President and Chief Medical Officer, CLL Society

Speaker: Neil E. Kay, MD
Professor of Medicine
Staff Consultant and Career Scientist
Division of Hematology, Department of Medicine, Mayo Clinic

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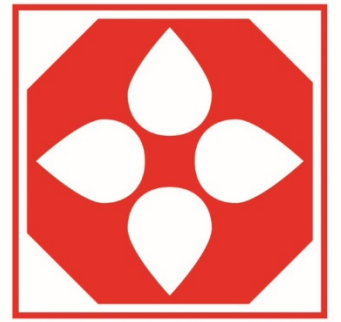
Just diagnosed: What do I need to know?



Neil E Kay, M.D.

2020

Objectives

- Diagnosis issues
- What is my prognosis if I present with early stage CLL (i.e. Rai 0-1)?
- What would be my expected standard of care over the next several years?
  - Assuming that there is no progression and need for therapy
- Monoclonal B Cell Lymphocytosis (MBL)
  - Lymphocytosis means an excess of blood lymphocytes
  - Diagnosis and clinical aspects

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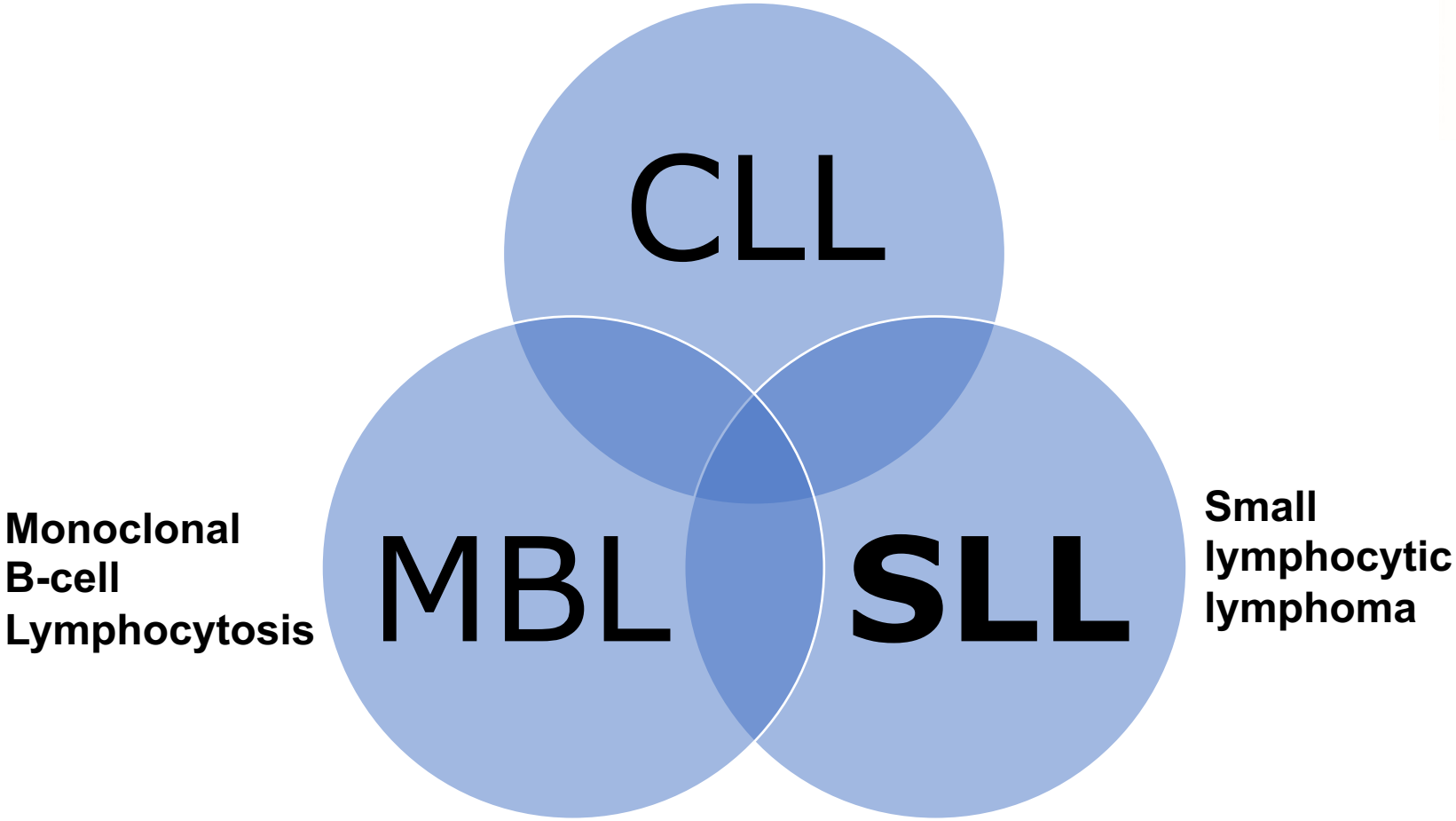
Nomenclature Comments



How Do I Know I Have CLL?

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- **CLL/SLL Diagnostic Criteria**

- **Must Show Presence of "monoclonal" B-lymphocytes**
  - **Flow cytometry of blood adequate for Diagnosis**
  - **Must show the presence of clonal (i.e. malignant) B cells**
  - **Absolute B lymphocytes > $5x10^9$/L**

- **MBL**

  - **Clonal population where absolute B lymphocytes ≤ $5x10^9$/L**

- **SLL**
  - **Lymph node biopsy if flow for diagnosis unrevealing**
  - **Adequate specimen, excisional (large chunk of tissue) biopsy preferred**

Hallek et. al. *Blood.* 2018; Vol. 131(25): pp. 2745-60

Familial CLL

- CLL has one of the highest familial-risks of disease among cancers.
- Family history of CLL is the strongest known risk factor for developing CLL.
- Individuals with a first-degree relative with CLL have an 8.5-fold increased risk of CLL.
- Prevalence of MBL in first-degree relatives of CLL patients is 13-18%
  - higher than the 5-10% prevalence found in the general population
- Estimate of 41 genetic variants for CLL susceptibility

1. JAMA. 2016;315(1):68-76
2. Journal of National Cancer Institute 2014;2014(48):41-51.
3. Haematologica. 2009;94(5):647-653.
4. Blood. 2002;100(7):2289-2290.
5. Br J Haematol. 2010;151(2):152-158.
6. Nat Commun. 2017;8:14175.

What is my Prognosis ?

Clinical Behavior in CLL

- **Wide variability in the clinical behavior and aggressiveness**
  - **Some patients live decades without treatment**
  - **Others develop symptoms quickly**

- **Doctors use a number of tools to try to predict future disease behavior for a given individual**
  - **Rai Stage**
  - **Prognostic tests**
  - **Models increasingly used**

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Clinical Behavior in CLL

- Most patients (>80%) diagnosed with stage 0 disease

- Now recognized even in stage 0 patients significant variation in clinical experience

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Stage and Clinical Outcome

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Rai Stage	Characteristic	Median Survival	2009* N=2397
0	Lymphocytosis only	150	168
I	Lymphadenopathy	101	120
II	Organomegaly	71	120
III	Anemia (Hg<11)	19	60
IV	Thrombocytopenia (<100)	19	76

*Mayo Clinic CLL Database 2009

Stage and Clinical Outcome

Median Survival of newly diagnosed CLL/SLL Patients (2008 criteria)

Regardless of whether they received treatment or not.

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Mayo patients seen from 1/1995-3/2020

Mayo Clinic CLL database (n=2,367)					
Rai Stage	Characteristic	N (Events)		Median OS (months)	Number at risk at 60 months
0	Lymphocytosis Only	993 (328)		154	534
I	Lymphadenopathy	951 (337)		140	503
II	Organomegaly	218 (93)		111	107
III	Anemia	105 (61)		57	35
IV	Thrombocytopenia	100 (51)		78	40

*Mayo Clinic CLL Database 2020

Integrating Multiple Markers: CLL International Prognostic Index

- Challenge to integrate multiple molecular biomarkers
- Pooled analysis 8 phase 3 trials ~3472 patients
- MV analysis: 5 factors independently associated survival

	points
Age>65	1
Clinical stage>Rai 0	1
IGHV (Immunoglobulin Heavy chain variable gene) Unmutated	2
B2M (beta 2 microglobulin) >3.5 mg/L	2
del 17p13 or *TP53* mutations	4

Add total points to yield a prognostic score from 0-10

Lancet Oncology: 17(6): 779-799, 2016.

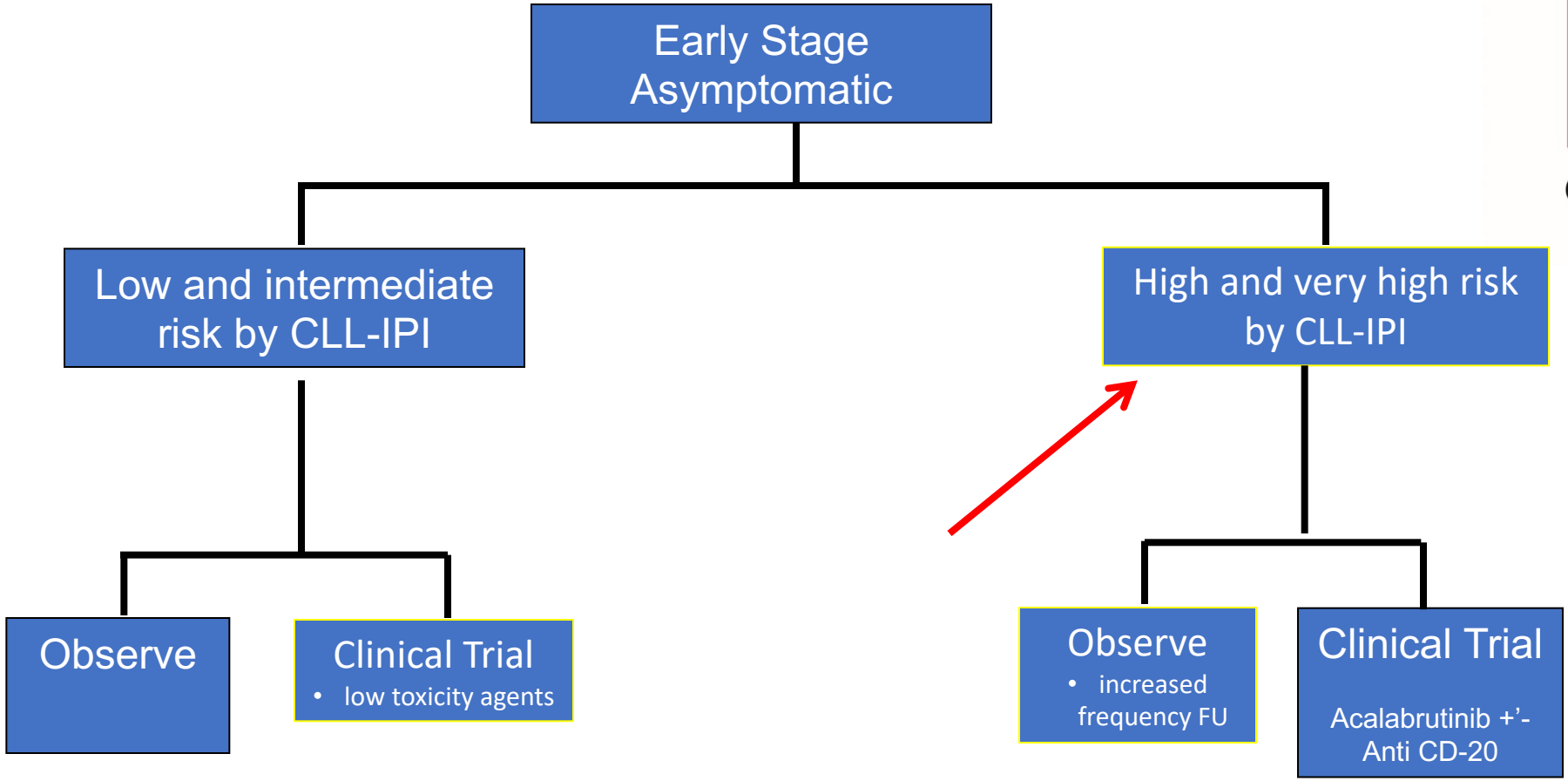
Risk group	Score	Patients, N (%)	Survival after 5 years, %	HR (95% CI)	*p* value
Low	**0 – 1**	340 (29)	93.2		
Intermediate	**2 – 3**	464 (39)	79.4	3.5 (2.5 - 4.8)	< 0.001
High	**4 – 6**	326 (27)	63.6	1.9 (1.5 - 2.3)	< 0.001
Very High	**7 – 10**	62 (5)	23.3	3.6 (2.6 - 4.8)	< 0.001

Mayo clinic has validated this for early stage CLL (0-1)

Why Use Prognostic Tools?

- **Counseling**
  - ***Knowing a good prognosis can be as important as knowing a bad one***
- **Follow-up**
  - **Risk of recurrence.**
- **Early Intervention if available**
  - **Clinical trials enrollment.**
- **Treatment Selection if progressive**
  - **Approach to 17p- patients**
    - **Chemoimmunotherapy less effective**

Early Stage Management



* Purine nucleoside analogues (e.g. fludarabine, pentostatin) are contra-indicated in patients with active autoimmune hemolytic anemia or ITP

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What is My Standard of Care During the Early Stage Phase?

CLL: Initial Evaluation

- **Recommended**
  - Hematology consultation [1]
    - Flow cytometry-to confirm diagnosis
    - Found differences in OS for CLL patients
      - Expertise matters!
  - Blood work
    - CBC/differential, platelet count (complete blood count)
    - Chemistries (help to assess liver/kidney function)
    - Check immunoglobulin levels (IgG, IgA, IgM)
      - 50% of all CLL but no association with OS
  - Genetic Studies
    - CLL FISH panel
      - detects all common genetic abnormalities in CLL
      - Should include an probe to exclude diagnosis of mantle cell lymphoma
    - IGHV mutation status (mutation levels of the gene)
      - Unmutated versus mutated status important to know

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1.Cancer. 2012 Apr 1;118(7):1827-37

CLL: initial Dx evaluation

- **<u>Consider</u>**
  - **TP53 sequencing (read the genetic code of the gene)**
    - aggressive clinical behavior inconsistent prognostic profile
  - **Bone marrow aspirate/biopsy**
    - Not necessary for initial workup
    - If low platelets , anemia or symptomatic
  - **CAT scan with contrast of chest, abdomen, pelvis**
    - **if primarily SLL type presentation**

*IGHV status does not change during disease course; there is no need to repeat assay

Follow up of Newly Diagnosed Asymptomatic CLL

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- Year 1
  - CBC and exam every 3-6 months*
    - More frequent if high risk FISH such as 17p- or p53 mutation is found
- Year 2 and beyond
  - CBC and exam every 6-12 months
    - More frequent if high risk FISH such as 17p- or p53 mutation
  - Intermittent evaluation of kidney and liver function
- *Additional testing as directed by symptoms*
  - Such as repeat serum Ig levels if recurrent bacterial infections
    - Immunoglobulins (IgG, IgA, IgM proteins that fight infections)

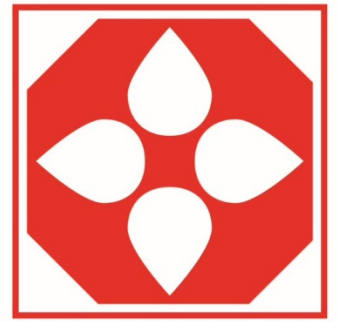
*Shanafelt et al, Annals of Internal Medicine, Vol 145:435-447

Indications to Start Therapy (IWCLL 2018)

- "B" symptoms
  - Fever, night sweats, weight loss
- Marrow failure
  - Anemia (Hgb <11)
  - Thrombocytopenia (Platelets <100,000)
- Progressive /symptomatic node/liver/spleen growth
- Autoimmune complications
  - Autoimmune Hemolytic Anemia (AIHA)
    - Antibodies directed at the red cells
  - Immune thrombocytopenic Purpura (ITP)
    - Antibodies directed at the platelets

Hallek et. al. *Blood.* 2018; Vol. 131(25): pp. 2745-60

Indications to Start Therapy (IWCLL 2018)



Need to emphasize that :

1. Recurrent infections are not an indication to start treatment.

2. Infections may transiently increase WBC counts, which may improve with resolution of the infection

3. May see transient increase in lymph nodes and/or WBC levels especially lymphocytes with insect bites!

- **Sole increase in total white cell count is not an indication for therapy**

Hallek et. al. *Blood.* 2018; Vol. 131(25): pp. 2745-60

Monoclonal B Lymphocytosis(MBL) Diagnostic Criteria

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- **MBL is classified by**
  - **specific clonal B-cell population in the blood**
    - **3 types- CLL-like MBL, non CLL-like MBL, or atypical MBL**
  - **size of the B-cell clone (low-count or high-count MBL)**

- **High Count MBL**
  - **Flow cytometry markers consistent with CLL**
  - **Has its own diagnostic code-finally**

- **Absolute B lymphocytes 3-5x10^9/L**
  - No abnormal blood counts or enlarged lymph nodes or enlarged liver/spleen by exam/CAT
  - No disease related symptoms

Hallek et. al. *Blood.* 2018; Vol. 131(25): pp. 2745-60

MBL: Initial Evaluation

- **Recommended**
  - Physical exam
  - CBC/differential
  - Flow cytometry
    - Confirm that this is CLL like clonal cell
  - Hematology consultation
    - To determine CLL vs non-CLL phenotype and the need for any additional evaluation at diagnosis
    - non-CLL phenotype MBL may require additional evaluation (e.g. bone marrow biopsy, CT scans)

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MBL: Incidence and Clinical Features

- High-count MBL has an incidence of 3.5 per 100,000 person-years [1]

- Shown to progress to CLL requiring treatment at a rate of ~1-2 % per year

- Complications much like CLL
  - Increased incidence of second malignancies [2]
  - Increased rates of serious bacterial infections
    - For both high count and low count MBL [3]

1. Clin Adv Hematol Oncol. 2013
2. Leukemia. 2016 Feb;30(2):331-6.
3. Leukemia. 2020 Mar 18. doi: 10.1038/s41375-020-0799-8. [Epub ahead of print] .

Follow Up of Newly Diagnosed MBL

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- CBC and physical exam in 6-12 months and then annually thereafter.
  - Additional testing may be considered for the development of symptoms or progressive anemia and/or low platelets
  - Patients with low count MBL (< 500/ul) rarely progress
  - Patients with high count MBL (>500/ul) progress to CLL requiring treatment at the rate of 1-2% per year

Rawstron, NEJM, 2008; Strati & Shanafelt, Blood, 2015

What About Supportive Care?

CLL Supportive Care Guidelines

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- Immunizations
  - Prevnar 13 followed by Pneumovax23 > 8 weeks apart*
  - Influenza (age appropriate)
  - Avoid live attenuated vaccines**
  - Recombinant shingles vaccine (Shingrex)

- Age-appropriate cancer screening and health maintenance
  - Applies to early stage patients as well
  - Second cancers tend to behave more aggressively in patients with CLL
    - Especially skin (non-melanoma type cancers)

- Skin cancer prevention
  - Increased skin cancer risk, patient education regarding sun protection
  - Whole body skin inspection/exam at diagnosis and every 1-2 years as appropriate

* Follow CDC guidelines regarding incorporation of Prevnar 13 in immunocompromised patients: (https://www.cdc.gov/vaccines/vpd/pneumo/downloads/pneumo-vaccine-timing.pdf)

** Shingles vaccine (Zostavax) is a live attenuated vaccine and is contraindicated in CLL per package insert. Other live attenuated vaccines (e.g. yellow fever) should generally be avoided.

CLL Supportive Care Guidelines (Pneumococcal Pneumonia)

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- Immunizations * **

- 1 dose PCV13 followed by 1 dose PPSV23 at least 8 weeks later, then another dose PPSV23 at least 5 years after previous PPSV23.
- at age 65 years or older, administer 1 dose PPSV23 at least 5 years after most recent PPSV23.

- Special note: only 1 dose PPSV23 recommended at age 65 years or older

- Follow CDC guidelines regarding incorporation of Prevnar 13 in immunocompromised patients: (https://www.cdc.gov/vaccines/vpd/pneumo/downloads/pneumo-vaccine-timing.pdf)

** Recommended Adult Immunization Schedule by Medical Condition https://www.cdc.gov/vaccines/schedules/hcp/imz/adult-conditions.html

Vaccine Cautions

Vaccine	Vaccine Type
Okay to give in CLL	
Diphtheria toxoid	Toxoid
Hepatitis A	Protein
Hepatitis B	Protein
Haemophilus influenzae (Hib) polysaccharide	Polysaccharide
Hib congjugate	Polysaccharide-protein conjugate
Influenza	Killed, subunit protein
Japanese encephalitis (inactivated)	Killed, viral
Meningococcal polysaccharide	Polysaccharide
Meningococcal conjugate	Polysaccharide-protein conjugate
Pertussis, whole cell	Killed
Pertussis, acellular	Protein
Pneumococcal polysaccharide	Polysaccharide
Pneumococcal conjugate	Polysaccharide-protein conjugate
Polio Salk	Killed viral
Rabies	Killed viral
Tetanus toxoid	Toxoid
Typhoid polysaccharide (injectable)	Polysaccharide
Contraindicated in CLL	
Influenza intranasal	Live attenuated viral
Measles	Live attenuated viral
Mumps	Live attenuated viral
Polio Sabin	Live attenuated viral
Rubella	Live attenuated viral
Tuberculosis (BCG)	Live mycobacterial
Oral typhoid	Live attenuated bacterial
Varicella (chickenpox)	Live attenuated viral
Varicella (zoster)	Live attenuated viral
Yellow fever	Live attenuated viral

Whitaker J,Clin Adv Hematol Oncol. 2014 Jul;12(7):440-50.

Shingrix Vaccine

- 99% of people over 50 years of age are living with the virus that causes shingles.
  - 1 in 3 people will get shingles in their lifetime

- The older live vaccine (Zostavax) is contra-indicated

- SHINGRIX is an FDA-approved vaccine for the prevention of shingles (herpes zoster) in adults 50 years and older.
  - A series of 2 doses of SHINGRIX are given on an initial and subsequent 3 month schedule by intramuscular injection

Shingrix trial for CLL ; ClinicalTrials.gov Identifier NCT03702231

Additional Considerations

- IVIG
  - If hypogammaglobulinemic and recurrent bacterial infections
    - 0.3-0.4 grams/kg per month
- Antiviral and Pneumocystis Prophylaxis
  - if on purine nucleosides, alemtuzumab or high dose steroids
    - During therapy and for a minimum of 6 months following
- PET Scans
  - Although not need for routine monitoring, PET scans are useful for evaluation of suspected Richter's transformation or secondary development of Hodgkin's lymphoma and are appropriate in routine practice for that purpose.
- Transfusions
  - Due to an increased incidence of transfusion associated GVHD, irradiated blood products should be used in patients with prior purine nucleoside or alemtuzumab exposure.

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Summary

- Most Early Stage CLL will have no need for therapy for years
- New tools to predict risk for progression
- Very important to be aware of clinical complications such as predilection for serious infections and second cancers
- Supportive care can be helpful for prevention and management of clinical issues

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Pneumococcal Vaccines

PPSV23 Vaccine History (number of previous doses)	Recommendations		
0	PCV13 first, followed by PPSV23 ≥ 8 weeks later	Second PPSV23*	PPSV23 at ≥ 65 years* Adults who received a dose of PPSV23 at age ≥65 years do not need another dose.
1	PCV13 ≥ 1 year after PPSV23	Second PPSV23 ≥ 8 weeks after PCV13*	
2	PCV13 ≥ 1 year after PPSV23		

Additional doses of PPSV23 should be administered ≥5 years after previous PPSV23 dose, if under the age of 65 years.

PPSV23 = 23-valent pneumococcal polysaccharide vaccine

PCV13 = conjugated 13-valent pneumococcal vaccine

Whitaker J,Clin Adv Hematol Oncol. 2014 Jul;12(7):440-50.

Audience Questions & Answers

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