Evaluation of Lymphocytosis & Diagnosis of Chronic Lymphocytic Leukemia (CLL)

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Overview

- Evaluation of lymphocytosis
- Diagnostic criteria for CLL and related conditions
- Rai staging of CLL
- Health maintenance for CLL patients

Mr. Smith

- Mr. Smith is a 58 y/o man with hypertension and type 2 diabetes who comes for a routine visit
- He is feeling well
- Physical exam is unremarkable
- His hypertension is well-controlled
- He has a fasting lipid panel and a CBC

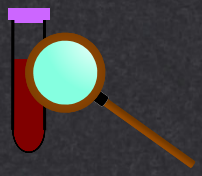
J. Smith	11-1-2019	
Complete Blood Count		
WBC*	17.2 k/uL	H
Hgb	15.1 g/dL	
Plt	247 k/uL	
Differential		
Neu	2.1	
Lym*	14.4	H
Mono	0.4	
Eos	0.2	
Baso	0.1	

Differential Diagnosis of Lymphocytosis

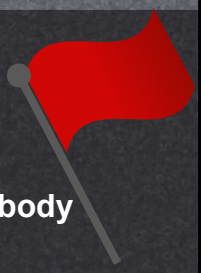
- Infectious mononucleosis (EBV or CMV)
- Viral infections (eg. HIV, influenza)
- Certain non-viral infections (eg. *bartonella henselae*, tuberculosis)
- Inflammation or trauma
- Prior splenectomy
- Lymphoproliferative disorders (eg. T-LGL, CLL, lymphomas)

Clues From the CBC

- Determine if relative (%) or absolute (cells/uL) – *relative lymphocytosis is rarely pathologic*
- Review any comments from the technologist or pathologist
- Review the peripheral blood smear
- Are there other abnormalities such as anemia, thrombocytopenia, or neutropenia?



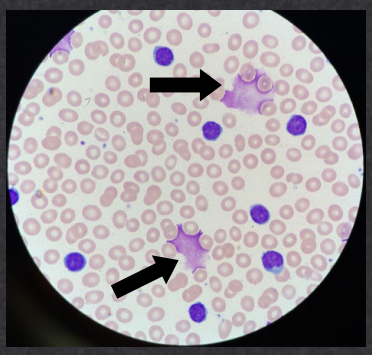
"Red Flag" Features



- Lymphadenopathy or splenomegaly on exam
- Constitutional symptoms
  - Rapid or unintentional weight loss (≥20% body weight)
  - Drenching night sweats
  - Fatigue limiting daily activities without other cause
- Signs of bone marrow failure such as anemia or thrombocytopenia
- Abnormal circulating cells in the peripheral blood
- Absolute lymphocyte count ≥30 k/uL and/or persistent on repeat testing months apart

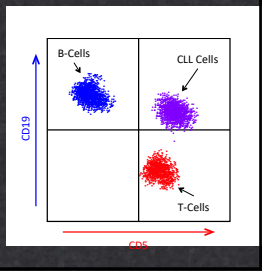
Mr. Smith returns in 6 weeks

- He feels well with no fatigue
- On exam
  - No enlarged lymph nodes
  - No splenomegaly
- Repeat CBC was similar
- Peripheral blood has mature appearing lymphocytes and smudge cells (arrows)
- Flow cytometry is recommended



Flow Cytometry

- Technique for immunophenotyping of blood cells
- White blood cells are marked with antibodies linked to fluorochromes to detect specific antigen markers (eg. CD20 or CD5)
- Cells are passed by a laser to determine which fluorescent markers are present
- Determines the types of white blood cells
  - T-cells (CD4+ and CD8+ counts)
  - B-cells
  - Myeloid cells
  - Blasts, leukemic cells, or other abnormal cells



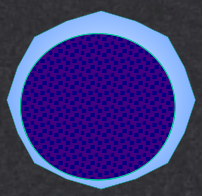
Mr. Smith's flow cytometry results

- The majority of B-cells were clonal with a "CLL-like" immunophenotype: (CD19+, CD5+, CD20^{dim}, CD23+, kappa light chain+, FMC7-)
- The clonal lymphocyte count was 11.2 k/uL
- Impression says "consistent with chronic lymphocytic leukemia"

- He asks if he has leukemia and what to do next

Diagnostic Criteria for CLL

- Presence of ≥5,000 u/L clonal B-lymphocytes in the blood
  - Persistent for >3 months
  - Clonality confirmed by light chain restriction
- Clonal cells have a "CLL immunophenotype"
  - B-cell antigens (CD19, CD20, and CD23) with CD5
  - Low/dim surface immune globulin, CD20, and CD79b
  - Restricted to kappa or lambda light chain expression



Hallek et al., Blood 2018

CLL & Related Diagnoses

Diagnosis	CLL Clone ≥5k	Enlarged Lymph Nodes	Enlarged Liver or Spleen	Cytopenias due to Marrow Infiltration
CLL	Required	+/-	+/-	+/-
SLL	-	Required	+/-	-
MBL	-	-	-	-

MBL = Monoclonal B-Lymphocytosis, SLL = Small Lymphocytic Lymphoma

- **MBL <u>cannot</u> be causing any signs or symptoms of disease**

Hallek et al., Blood 2018

Chronic Lymphocytic Leukemia (CLL)

- Chronic B-cell lymphoid malignancy
- Median age at diagnosis is approximately 65
- Most prevalent leukemia in adults
- Median survival is good and can be predicted by cytogenetic testing
  - Poor risk = years (median for del17p = 32 months)
  - Good risk = decades (median for del13q = 133 months)
- Survival today is likely improved over historical estimates with newer more effective treatments such as oral targeted agents

Hallek et al., Blood 2018; Dohner et al., NEJM 2000

Chronic Lymphocytic Leukemia (CLL)

- People who are asymptomatic should be observed
- Treating people at diagnosis does not improve survival
- Over the course of the disease people develop
  - Enlarging lymph nodes
  - Increasing lymphocyte count – *even up to 300-400 k/uL can be ok*
  - Cytopenias due to marrow infiltration with leukemia
  - Constitutional symptoms in some cases
- If these become a problem treatment is started
- Some people never require treatment!

Hallek et al., Blood 2018

Small Lymphocytic Lymphoma (SLL)

- The lymphoma version of CLL
- Has the same immunophentype as CLL but without ≥5,000 /uL CLL-cells in the blood and has enlarged lymph nodes
- Prognostic features and outcomes are the same as with CLL
- Treated with the same therapies as CLL
- Can generally be considered together with CLL

Hallek et al., Blood 2018

Monoclonal B-lymphocytosis (MBL)

- Not a cancer
- Common in the elderly
  - Incidence increases with age (5.1% of people age 60-80)
- Can have a "CLL-like" or "non-CLL-like" immunophenotype
  - More is known about "CLL-like" MBL
  - "Non-CLL-like" may eventually progress to other lymphomas
- Can be low-count (<0.5 k/uL) or high-count (≥0.5 k/uL)
  - High-Count progresses to CLL at a rate of ~1-2% per year
  - Low-count almost never progresses to CLL

Rawstron et al., NEJM 2008; Strati et al., Blood 2015

Rai Staging of CLL

- Requires a physical exam and CBC
- Higher stage correlates with shorter overall survival

- Bone marrow biopsy and CT scans are not needed for staging
- Both should only be used to evaluate symptoms or findings
  - Bone marrow biopsy to evaluate unexplained cytopenias
  - CT scans for abdominal pain or palpable masses

Rai et al., Blood 1975; Hallek at al., Blood 2018

Rai Staging

Rai Stage	Finding	Modified Rai Classification
0	Lymphocytosis	Low Risk
I	Lymphadenopathy	Intermediate Risk
II	Splenomegaly and/or Hepatomegaly	
III	Anemia (<11 g/dL)	High Risk
IV	Thrombocytopenia (<100 k/uL)	
Category is assigned based on highest risk finding		

Rai et al., Blood 1975; Hallek at al., Blood 2018

Advising Mr. Smith on his diagnosis of CLL

- You tell Mr. Smith he has chronic lymphocytic leukemia and refer him to a hematologist
- You make sure to tell him:
  - The expected survival is many years to potentially decades
  - He may <u>not</u> need treatment right now
  - Treatments for CLL are highly successful and often have only mild side effects
  - This is the most prevalent leukemia in adults, so he is not alone
- You plan to see him back after his appointment

Mr. Smith returns after the hematologist visit

- He reports having a positive initial visit
- Confirmed CLL – Rai stage 0
- Blood work done to learn more about the nature of his CLL
- No treatment was recommended
- His return visit with the hematologist is in 3 months

- The hematologist recommended he discuss health maintenance with you, specifically cancer screenings and vaccinations

Implications for Health Maintenance

- People with CLL have inherent immune dysregulation
- Higher risk for autoimmune disease and complications from decreased immune function
- In one study (n=795) estimated 20-year occurrences
  - Major infection – 48%
  - Second Cancer – 42%
  - Autoimmune Disease – 29%
- Since CLL-specific survival is generally good therefore these other risks are an important cause of morbidity and mortality

Visentin et al., European Journal of Cancer 2017

Risk of Second Cancers is Increased

- CLL increases risk for other types of cancer
- In large cohort studies overall risk for second cancer was increased (HR 1.96, SIR 2.17)
- Highest risk was for
  - Squamous Cell Carcinoma of the Skin (HR 24.58 - non-invasive)
  - Merkle Cell Carcinoma (HR 14.36)
  - Non-hodgkin lymphoma, "Richter's syndrome" (HR 7.16)
- Therapy related cancers after chemotherapy for CLL are also occur - *~5% rate of AML/MDS after FCR*

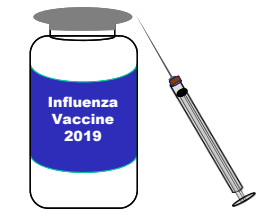
Zheng et al., BJH 2018; Royale et al., British Journal of Cancer 2011; Thompson et al., Blood 2016

Approach to Cancer Screening in CLL Patients

- Recommend all age appropriate cancer screenings
- Should be based on the individual patient's risk factors
- If you are considering stopping screening based on age or lower risk take the CLL into account
- Annual skin exam is recommended due high risk of non-melanoma skin cancers and increased risk for melanoma

Vaccination Recommendations

- Vaccines have decreased efficacy in CLL patients but <u>should still be given</u>
- CDC has recommendations for vaccination in immune compromised individuals
- Live vaccines should be avoided
- Always consider
  - Annual influenza vaccination
  - Pneumococcal vaccines
  - Shingrix (has some efficacy and is killed unlike Zostavax)



Dagnew et al., Lancet Infectious Diseases 2019

Considerations for MBL Patients

- Patients are followed at least annually as they may progress to CLL
- Same health risks as CLL compared to healthy controls
  - Hospitalization for infection (HR 3.0, p=0.001)
  - Diagnosis of non-hematologic cancer (HR 2.36, p=0.04)
  - Autoimmune Diseases
- Cancer screening and vaccination recommendations are the same as for CLL patients

Rawstron et al., NEJM 2008; Strati et al., Blood 2015; Moreira et al., Leukemia 2013; Solomon et al., Leukemia 2016

Take Home Points

- Lymphocytosis has many causes
- Patients with persistent absolute lymphocytosis and/or “red flag” features should be further evaluated, usually with flow cytometry
- CLL is the most prevalent leukemia in adults
- Expected survival for CLL patient is many years
- CLL does not need treatment at diagnosis
- CLL, SLL, and MBL patients have a higher risk for second cancers and infections and need strategies to manage this risk

My Patient has CLL—Now What?

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Objectives

- To discuss prognostic factors in CLL
- To discuss the rationale for watch & wait, and indications for treatment
- To briefly discuss initial therapies and side effects you might observe during long-term oral therapies.
- To discuss other considerations when managing patients on therapy for CLL

How is prognosis assessed in the asymptomatic CLL patient?

At Mr. Smith's visit to see you, he remarks that he has noted some laboratory tests returned via MyChart. He has an appointment with his hematologist again next week, but wonders if you can tell him anything about the results in the meantime…

- IGHV unmutated (0.3%)
- FISH shows trisomy 12 as the only abnormality
- B2M in normal range
- TP53 without mutation

Natural History of CLL

- Heterogeneous disease with survival ranging from months to 25+ years from diagnosis
- Prognostic factors commonly used
  - Stage
  - Lymphocyte doubling time
  - Beta 2 microglobulin
  - IGHV mutational status
  - FISH/Stimulated karyotype

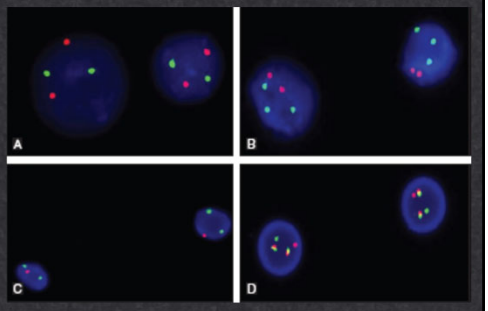
IGHV Mutational Status

- Indicates the divergence of the immunoglobulin heavy chain variable region from the germline sequence.
- Higher levels indicate greater amounts of normal somatic hypermutation, and suggest a more mature precursor cell
- Currently the strongest predictor of prognosis

Hamblin, Blood 1999

Cytogenetics & Fluorescence In Situ Hybridization

Metaphase spread



A. Normal
B. Trisomy
C. Deletion
D. Translocation

Implications of FISH/Cytogenetics on Prognosis

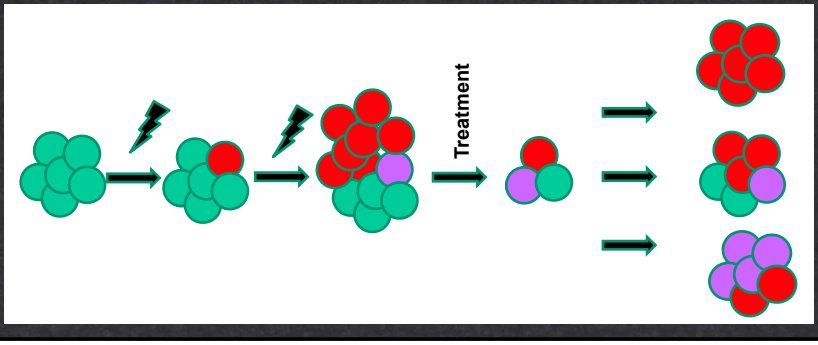
- Del(13q), the most common abnormality, indicates indolent disease when detected as the sole abnormality (>50% of pts)
- Trisomy 12 indicates intermediate prognosis (~30% of pts)
- Del(11q) results in loss of the tumor suppressor ATM and is associated with more aggressive disease (~20% of pts)
- Del(17p) results in loss of the tumor suppressor TP53 and is associated with poor prognosis (~10% of pts)
- Complex karyotype (≥ 3 abnormalities) is associated with high risk disease

TP53 Mutation

- Mutations are common in CLL, but most mutations are shared infrequently (2-5% of patients)
- TP53 mutations are seen in about 10-15% of patients at diagnosis.
- 80% of the time, mutations co-exist with del(17p)
- These indicate poor prognosis

Can Prognosis Change Over Time?

- IGHV mutational status does not change
- Cytogenetic abnormalities and gene mutations can, a process called clonal evolution
  - TP53 abnormalities seen in 10% at baseline, but ~40% later



What do we tell Mr. Smith?

- With IGHV unmutated disease and trisomy 12, he has an intermediate prognosis
- He will likely require therapy, average time to first treatment about 3 years
- Do not refer to survival estimates on the internet—they are wrong and do not take into account newer therapies

Indications for Therapy

Category	Reasons for Treatment
CLL-related symptoms	• Significant B symptoms (eg, night sweats, weight loss, fever without infection, severe fatigue)
Tumor burden	• Progressive lymphadenopathy • Progressive splenomegaly Lymphocyte doubling time <6 months (if ALC >30 x 10^9/L) • Threatened end-organ function (eg, enlarged lymph node obstructing biliary tree)
Bone marrow failure	• Progressive anemia (Hgb <11 mg/dL) • Progressive thrombocytopenia (platelets <100K)
Immune dysfunction	• Autoimmune anemia and/or thrombocytopenia poorly responsive to corticosteroids or other standard therapy

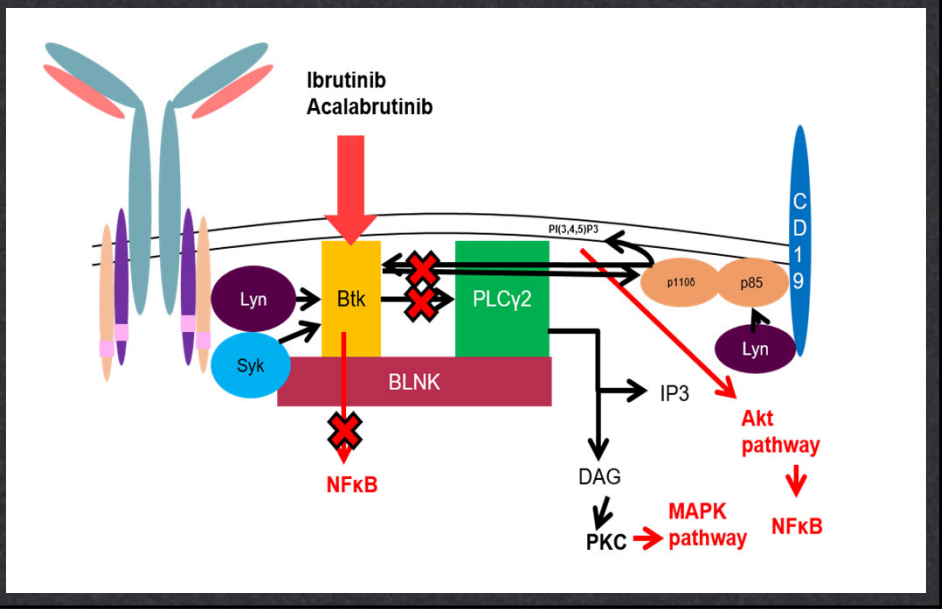
Why Don't We Treat at Diagnosis?

- Multiple clinical trials have investigated this question—none yet have shown a survival advantage to early treatment.
- This remains a question of interest, especially with advances in prognosis (so high risk patients can be targeted) and with newer better tolerated therapies.

Back to Mr. Smith…

- Four years after diagnosis, Mr. Smith begins to have fatigue and progressive lymphadenopathy. He discusses options with his hematologist and starts therapy with ibrutinib. Very quickly after starting, his lymph nodes shrink and his fatigue improves.
- 6 months into treatment, he presents to the office for a routine visit, and you find his blood pressure to be elevated (164/86). He asks whether his ibrutinib is causing this…

What is this drug?



What is this drug?

- Ibrutinib is an inhibitor of Bruton's Tyrosine Kinase (BTK)
- In relapsed CLL, median PFS 52 months
- As frontline therapy, PFS duration unknown, but > 88-90% at 2 years.

Cardiac Complications of Ibrutinib

- Hypertension
  - Only toxicity that becomes more common with longer duration of therapy
  - Incidence variable in studies—institutional data of >500 patients showed incidence 78%
  - Treatment of HTN decreases incidence, optimal agent not known
- Atrial Fibrillation
  - Incidence 10-15%, much more common in older patients
  - Can continue therapy and manage arrhythmia, also consider switching therapy
- Ventricular Arrhythmia
  - Very uncommon, but risk is present
  - Atrial fibrillation is only confirmed prognostic factor

Other Toxicities Encountered

- Joint pain
  - Steroids and dose interruptions can help
- Nail and hair changes with long-term treatment
  - Biotin can be beneficial
- Bleeding
  - Ibrutinib contraindicated with warfarin
- Infections
  - Specific risk of aspergillus due to BTK inhibition. Questionable risk of PJP

- Drug interactions are important with this and other targeted anti-cancer agents
  - Check with pharmacist or hematologist before prescribing new medications to avoid interactions

Is this something I really need to know?

- CLL patients are living longer as therapies are becoming more effective and better tolerated
- Many targeted therapies in CLL and other diseases have unpredictable side effects, and patients (and physicians) may not know what is drug related and what is not
- Collaboration between hematologists, other subspecialists, and especially primary care doctors is necessary to optimally care for these patients

Take Home Points

- CLL is a heterogeneous disease; genomic factors can better refine prognosis for individual patients
- Therapy in CLL is initiated at the onset of symptoms, there is not currently a role for early treatment
- Initial therapy is usually oral targeted therapy
- As patients are living longer and therapies are improving, increased collaboration is important to manage patients with CLL


The James Cancer Hospital and Solove Research Institute