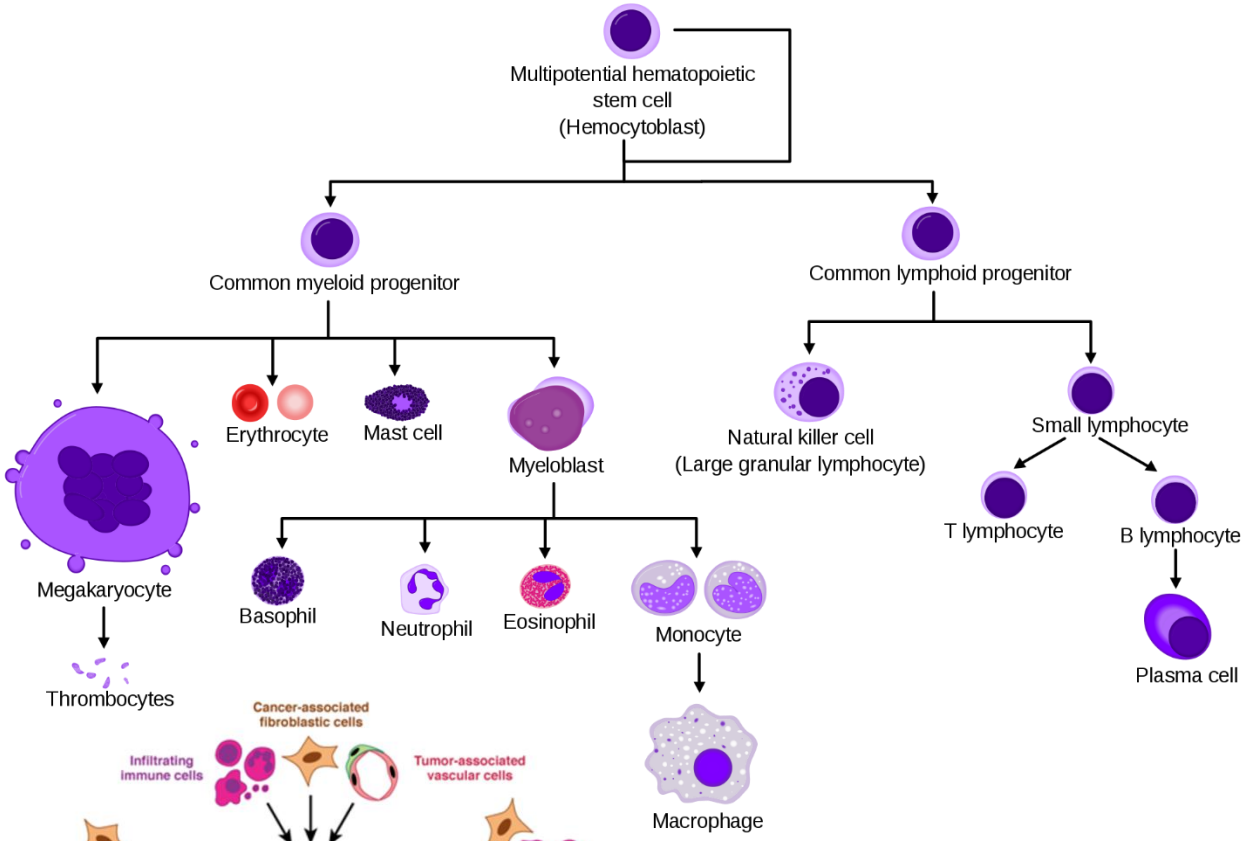
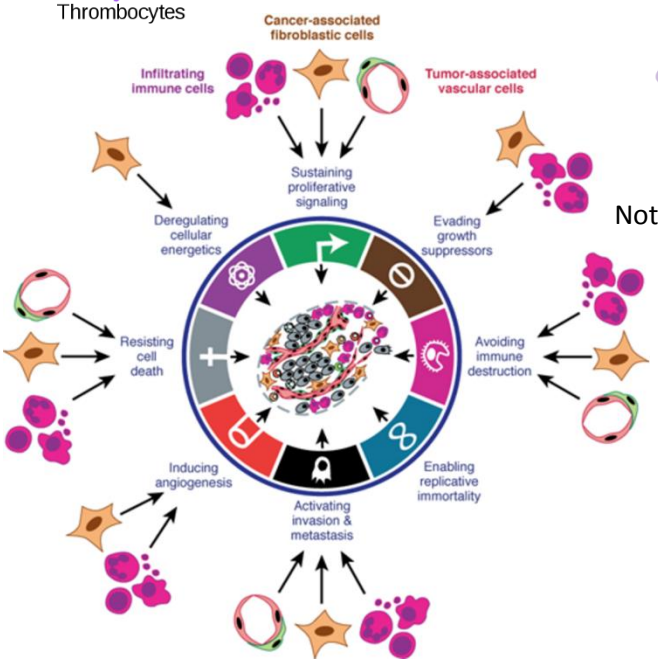
Academic Half Day: Hematologic Malignancy

Preceptor Copy

1:00-1:15 – Theory Burst
1:15-2:30 – Pathophysiology Exercise
2:30-2:40 – Questions and Break
2:40-3:30 – Cases 2
Fin.

Hematopoietic Stem Cell Map

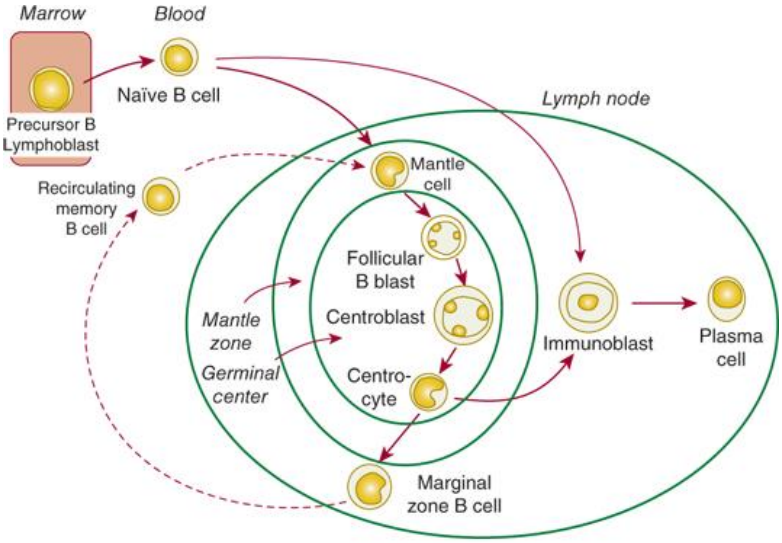


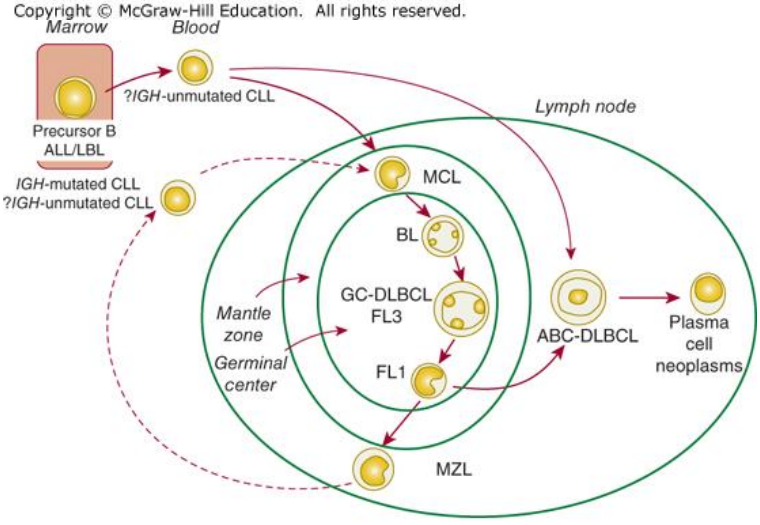


Notes:

Lymphocyte Maturation

Notes:





Questions to lead the physiology exercise

Objective: derive the symptoms and lab abnormalities from the physiology, we are lesion localizing!

1. **Have them fill out the chart with the names, make sure to stress the different lineages of lymphoid and myeloid cells**
2. **What the common pathophysiology amongst all the hematologic malignancies at the most basic level?**
    - **a.** There is a mutation somewhere along the pathway that creates a weird clone cell that does not behave normally
    - **b.** That mutation may make cell reproduce more, not be able to differentiate, die early, etc – see the hallmarks of cancer chart. Discuss some of these mechanisms. Depending on what kind of mutation and where it is, we get different phenotypes of liquid malignancies. Throughout the physiology exercise, refer to this chart and keep in mind what kind of mutation may cause the issues?
3. **There is a "lesion" in the pathway near the common myeloid progenitor cell, it is a (9;22) translocation creating an endless activated tyrosine kinase (BCR-ABL) resulting in unchecked reproduction. What would you expect on a CBC?**
    - **a.** Key point here is that *they can still mature*
    - **b.** Increased amounts of *different mature myeloid cells* - thrombocytosis, basophils, neutrophils – *and immature cells* – metamyelocytes, myelocytes, bands
4. **What clinical complications do you expect from this? Symptoms? Physical Exam?**
    - **a.** Key point: the cells that are being made are largely normal because they are differentiating normally so you do not get symptoms from cellular dysfunction until there is a blast crisis and you get immature malfunctioning cells
    - **b.** You largely get symptoms from mass effect of the large spleen, weight loss from increase metabolic demand of cancer, and bone marrow hypercellularity -> anemia/fatigue
    - **c.** Weight loss from the malignancy, early satiety/abd fullness due to splenomegaly
    - **d.** Physical exam: Splenomegaly, bruising, poor fitting clothes, pallor. Not as much lymphadenopathy in chronic phase – usually in CML this is seen in accelerated/blast phases
5. **How many blasts should you see in CML?**
    - **a.** Not many in the chronic phase because the blasts are differentiating to more mature cells. CML comes in three phases
        i. Chronic (Blasts < 10%), increased % of basophils
        ii. Accelerated (Blasts 10-20%), basophils > 20%
        iii. Blast crisis (Blasts >20%)
6. **Using the chart, how are Polycythemia Vera, Essential Thrombocytosis, and Primary Myelofibrosis similar and different?**
    - **a.** Key Point: Have them lesion localize each to different lineages. JAK2 is often mutated in these but it more depends on where the mutation is in the pathway.
    - **b.** PV – Increased erythrocyte precursors
    - **c.** ET – Increased megakaryoctes -> platelets
    - **d.** PMF - Increased megakaryocytes making lots of fibroblast growth factor causing fibrosis of the bone marrow

    i. You can ask them what kind of physical exam findings they would expect from PMF – if the bone marrow is significantly fibrotic that effective erythropoiesis cannot occur, where else can this occur? They get massive spleens. Compared to MSD, where you also get anemia but there is erythropoiesis -> such significant splenomegaly is less common.

7. **Knowing that all these diseases have a common general pathophysiology, how do we make sense of a disease that presents with a worsening macrocytic anemia from a pathophysiology perspective? (where and what kind of lesion do we look for?)**
    a. Key point: This is a clonal disorder!
    b. Myelodysplastic syndromes (MDS) represent a collection of hemapoietic neoplasms characterized by abnormal differentiation, dysmorphology, and resultant blood cytopenias. The hallmarks of these clonal disorders include exaggerated apoptosis of hematopoietic precursors in the marrow, common chromosomal abnormalities, frequent somatic gene mutations, and a variable predilection to undergo clonal evolution to acute myelogenous leukemia (AML).
    c. The clinical course of patients with MDS is variable and ranges from relatively indolent clonal cytopenias (e.g., refractory anemia) with a low rate of AML transformation, to more aggressive disease defined by an increased proportion of marrow myeloblasts, oligoblastic myelogenous leukemia (refractory anemia with excess blasts), and a greater risk of progression to AML.
    d. MDS are closely related to other myeloid neoplasms such as AML and some myeloproliferative neoplasms. The dysmorphia of neoplasia (commonly referred to as dysplasia in describing MDS) refers to the abnormal morphology than can be observed in neoplastic mature blood cells and maturing marrow erythroid, granulocytic, and megakaryocytic precursor cells, and is one of the distinguishing characteristics of MDS.
8. **What would happen if there was another mutation and the myeloblasts could no longer mature?**
    a. More blasts -> crisis! By definition >20% blasts is AML. However, there are acute leukemias that do not meet that definition (APML can have <20% blasts)
    b. What is this called? Have them identify this as a transformation from MDS to AML.
    c. Key Point: all these hematologic malignancies are related to some degree and can progress to AML with an additional mutation, it's a spectrum
9. **Special case: In AML subset of APML, you have promyelocytes that can't differentiate, we have a medicine that can cause them to differentiate, what is it?**
    a. ATRA
10. **Based on the natural life of a neutrophil/myelocyte, what complications could you expect to see after giving ATRA?**
    a. If they can't answer here, walk through what neutrophils do – they roll around the inside of blood vessels, are sticky and big, they release cytokines, and they prefer to marginalize in the *lungs*.
    b. Differentiation syndrome: sudden immune reconstitution and cytokine release from transformed neutrophils. Presents like sepsis, can have fever, edema, hypoxemia and pulmonary infiltrates, hypotension and serositis.
    c. Treatment is with Dexamethasone 10 mg IV Q12H.

11. **What could you see on a CBC during a blast crisis?**
    a. Guide them here: is there are a lot of blasts, what would you see in the bone marrow? Lots of blasts. Is there room to make other cells? Not often -> cytopenias.
        i. Almost always low retic count, anemia, and 50% of the time thrombocytopenia < 50 plts
    b. How many absolute neutrophils would you have? Often this is very low (neutropenic!) because they do not have mature cells, tons of blasts
12. **What happens if you have high levels of blasts? Upwards of 100k**
    a. Discuss hyperleukocytosis (5% of people present this way)
    b. Similar pathophysiology to differentiation syndrome!
        i. Local hypoxemia may be exacerbated by the high metabolic activity of the dividing blasts and the associated production of various cytokines causing end organ damage
        ii. Sticky cells big cells blocking vasculature and causing end organ damage
    c. *Symptoms*: The circulations of the CNS, lungs, and penis are most sensitive to the effects of leukostasis. Intracerebral hemorrhage from vascular occlusion, invasion, and disruption, sometimes complicated by thrombocytopenia and vascular insufficiency are the most virulent manifestations of the syndrome. Dizziness, stupor, dyspnea, and priapism may occur.
13. **Why do you not get hyperleukocytosis as often with lymphocyte malignancies?**
    a. They are smaller, hang out in the lymphoid organs, and are less metabolically active
14. **What does a B-cell do after it is made in the bone?**
    a. Have them walk through the life cycle of a b-cell and talk about what happens in each area
    b. Immature B-cells - float around, inactive, need mature in a lymphoid organ, they need some antigen presented to them
    c. Mantle Zone - In the secondary follicle, it is outside the germinal center where immature b-cells gather
    d. Germinal Center - Immature b-cells get presented antigens and go through **somatic hypermutation** to make accurate antibodies that will only attack the antigen they are presented with.
    e. Marginal Zone - Much less active zone of replications, where the b-cells go next and differentiate into plasma cells (via immuno*blasts) or* memory b-cells
15. **Lesion localize the lymphomas**
    a. CLL - early b-cells
    b. Mantle Cell
    c. Burkitt's (early germinal center lymphoma, very aggressive)
    d. Germ Center DLBCL
    e. Follicular Lymphoma - spectrum depending on how far through the mutation process the lymphoid is – Follicular I is near the end with more mature cells, Follicular III is closer to the DLBCL in mitotic activity

f. Activated B-Cell DLBCL - from immuno*blasts* when b-cells are differentiating into plasma cells

g. Marginal Cell Lymphoma - post-germinal center where the activated cells hang out. Gastric MALTomas are Marginal Cell Lymphomas. Can discuss why some infections can pre-dispose to lypmhomas – if the infection is not cleared and constantly activating b-cells -> mutation -> lymphoma. Examples: EBV, H.Pylori, etc.

h. Hairy Cell Leukemia – circulation b-cell lineage

16. **What do you need to diagnose lymphoma diagnostically?**
    - **a.** Ask what kind of biopsy they want. We need the whole lymph node to see the architecture!
    - **b.** Flow Cytometry, CD – cluster of differentiation allows us to see what surface markers the cells have. These change as the B and T Cells mature.
    - **c.** Bone marrow biopsy: Practically all patients with Non-HL should undergo a BM aspiration and biopsy prior to the initiation of treatment as part of their staging evaluation.
17. **Based on the areas they are in, and the level of reproduction, try to predict which are characterized as "aggressive" and which are "indolent"**
    - **a.** What is happening in the mantle layer vs germinal center vs marginal zone?
        - **i.** In the mantle new b-cells are gathering to be ushered into the germinal center where they get exposed to antigens and undergo hypersomatic mutations to make great antibodies that are very specific.
        - **ii.** Ask them to think about where the lesion is – is it at a place where the cells are mutating and replicating a lot? Or is it a place there they are more stable and mature?
    - **b.** Indolent: CLL, Follicular Lymphoma, Marginal Cell Lymphoma, Hairy Cell Leukemia
    - **c.** Aggressive: Mantle Cell, Burkitt's, Germ Center DLBCL, Activated B-Cell DLBCL
18. **Returning to the most common leukemia – Chronic Lymphocytic Leukemia – what are some complications we could expect?**
    - **a.** Ask them to lesion localize it to circulating b-cells
    - **b.** B-cells make immunoglobin, if they are poorly functioning clones that pre-dominate, the IG are going to be deficient either in number or in function leading to autoimmune issues (ITP, AIHA) or increased infections (hypogammaglobulinemia).

Questions
and
Break

Mini Cases

1. **Patient is a 62 y/o M with a history of smoking, HTN, HLD, and DMII who presents to clinic with worsening fatigue over the last few months.** What is your differential? What additional history do you want? Physical exam? Labs? Other testing?

   Additional History: DOE, some chest pressure with exertion that is new over the last few weeks, pressure gets better with rest. No night sweats, chills. No weight loss. No constipation, cold intolerance. No clinical signs of bleeding.

   PE: Well appearing, NAD, dyspneic with exertion down the hall, some pallor, no splenomegaly, no LAD, normal thyroid
   CBC: WBC 12, Hgb 9, MCV 98, Plt 220, diff: L N B E Blast
   TSH: Normal
   EKG: LVH
   Stress Test: positive -> LHC with critical stenosis -> stented and started on goal-directed therapy -> improved symptoms
   Dx: CAD

   Learning Objective: These malignancies can present with vague symptoms, this patient could also easily have a myeloid neoplasm. *Ask them how they would've changed his labs and exam to match a diagnosis of CML, how to make the exam and CBC match MDS, how to make the exam and CBC match PMF.*

2. **Patient is a 68 y/o Vietnam Vet who presents to the VA with shortness of breath, productive cough, fevers and chills. CXR showed left lower lobe consolidation.** What is your differential? What additional history do you want? Physical exam? Labs? Other testing?

   Additional History: He was exposed to Agent Orange (associated with CLL). They should ask about recent antibiotics or hospitalizations -> he was recently admitted with *S. Pneumonaie* pneumonia, this his 4th admission this year for pneumonia. He has had some night sweats and chills, has been losing weight over the last few years. He feels like he is eating less because he is getting full faster.

   PE: Uncomfortable appearing, tachypneic, NAD. Crackles LLL and dullness to percussion. Lymphadenopathy diffusely, enlarged spleen, no abd tenderness, no edema, normal heart sounds.

   CBC: WBC 45 Hgb 8, MCV 89, Plt 180: diff: L high N high B normal E normal Blast none
   EKG: normal
   IG LeveL: Low

Treating Hypogammaglobulinemia in CLL - It is universally present in patients with CLL and progressively worsens with advancing stage of the disease. Intravenous immunoglobulin (IVIG) at doses of 250 to 600 mg/kg administered every 4 to 6 weeks may result in a significant reduction of major infections requiring intensive supportive care and a modest reduction in the incidence of clinically significant infections. However, there is no significant improvement in survival.

Learning Objective: Goal is to notice that this patient keeps getting re-admitted and to look into it. CBC will show CLL. This is to review complications of CLL (recurrent infections 2/2 IG deficiency) Treatment, IVIG, this is not an indication for treatment of CLL.

3. **Patient is a 72-year-old with a history of CLL, COPD, CAD, and HTN who presents to the ED with worsening shortness of breath and fatigue over the last week.** What is your differential? What additional history do you want? Physical exam? Labs? Other testing?

   Additional History: Short of breath with exertion and at rest, no chest pain, no cough, fevers, or chills. He has had long standing night sweats and chills intermittently but have not changed for years. His family states that he looks pale. No hematemesis, no BRBPR, no melena. No NSAID or alcohol use. No abd pain.

   PE: Well appearing, pale, sitting upright in bed. CTAB, RRR, no murmurs. Enlarged spleen, and some lymphadenopathy. Rectal exam is negative for blood.

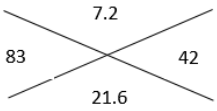
   CBC: WBC 142 Hgb 7, MCV 89, Plt 215: diff: L high N high B normal E normal Blast none
   Coombs: Positive
   LDH: high
   Haptoglobin: low
   Indirect Bilirubin: Elevated
   EKG: normal
   Slide: *** will add***

   Treating AIHA in CLL: Glucocorticoids (1-1.5mg/kg prednisone per day) are first line, result in initial clinical responses in 50 to 90 percent of patients. However, only approximately one-third of patients remain in long-term remission once the drug is discontinued. Less than 20 percent of adults with warm AIHA are cured by steroids alone. Rituximab can also be considered as a solo agent or in conjunction with steroids.

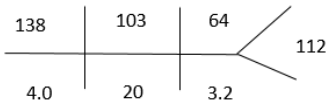
   Learning Objective: CLL complication – AIHA! Treatment, steroids, this is not an indication for treatment of CLL.

4. **Patient is a 82 y/o male with a history of MDS who presents to the ED with worsening severe fatigue, and new purple spots on his arms and legs. He has also noticed a new headache and blurry vision. His temp is 101.2. He is ill appearing, pale, and tachycardic to the 130's. You**

obtain a CBC with diff and BMP in office and decide to admit him to the hospital emergently for further evaluation.



Seg 12%
Band 6%
Lymph 7%
Metamyelocyte 15%
Myelocyte 2%
Promyelocyte 6%
Blasts 52%



Slides: *** will add***

Questions: which slide is normal, which is AML, which is APML, which is CLL, and which is CML

What are some of the complications of this diagnosis? You can discuss DIC here if APML, hyperleukocytosis, DIC, infections, TLS (what labs would they want?) and how you would approach each as below.

Infection - Broad spectrum ABx – include activity against pseudomonas. Vanc/Cefepime as he appears septic. He has a highly dysfunctional immune system and is at risk for opportunistic infections.
TLS: Uric acid, K, Ca, Phos, renal panel. Rasburicase, allopurinol for ppx (Tumor lysis syndrome – hyperuricemia, hyperkalemia, hyperphosphatemia, hypocalcemia, renal failure), fluids, do not replete calcium until phosphate is ok.
DIC – Check PT/PTT, fibrinogen, plt, hemoglobin.
Leukapheresis – especially if chemotherapy not immediately started. Leukostasis occurs in 10-20% of patients with AML. Extremely high WBC, hyperviscosity, and local hypoxemia from rapid oxygen utilization occur. Can present with acute-chest-like or stroke-like symptoms. A medical emergency as has a high mortality rate if left untreated.

Learning Objective: MDS transformation into AML, main objective here is to look at the slides and to think about the complications of patient's presenting with AML.

5. Patient is a 67 y/o with CLL who presents to clinic for routine follow up. What questions do you want to ask the patient about their CLL? What are the general indications for treatment?
Learning Objective: When to treat CLL

Additional History: He's been feeling more fatigued recently. No easy bruising or bleeding that he has noticed. He is eating well, no weight loss. No abdominal discomfort.

PE: Well appearing, pale. CTAB, RRR without murmurs. He has LAD and an mildly enlarged spleen.

CBC: WBC 258 Hgb 13, MCV 89, Plt 215
Diff: L high N high B normal E normal Blast none
EKG: normal

Indications for treatment in CLL:

Table 1. Rai classification system*

Stage	Description	Median survival (months)	Risk status (Modified Rai)
0	Lymphocytosis, lymphocytes in blood >15,000/mcL and >40% lymphocytes in the bone marrow	140	Low
I	Stage 0 with enlarged node(s)	100	Intermediate
II	Stage 0–1 with splenomegaly, hepatomegaly, or both	70	Intermediate
III	Stage 0–II with hemoglobin <11.0 g/dL or hematocrit <33%	20	High
IV	Stage 0–III with platelets <100,000/mcL	20	High

** Adapted from the 2008 NCI guidelines; BC Cancer Agency 2008 guidelines.*[3,4]

Therapy instituted at higher stages (3+) with a goal of palliation. Multiple chemotherapeutic agents available including newer agents like Ibrutinib as detailed in reading

For asymptomatic early stage (Rai 0-II) – Observation with labs Q3 mo