Hematologic Malignancies

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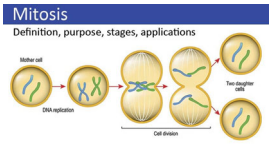
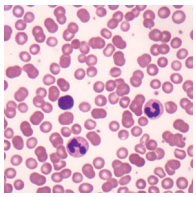
What is cancer?

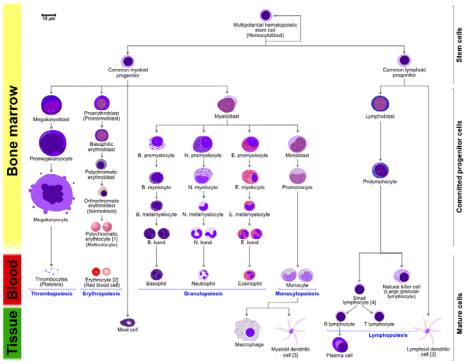
- The body is made up of small building blocks called cells
- Each of these cells has its own life cycle
- When a cell divides, it replicates its own DNA
- Mutations can occur during DNA replication which can cause the cell to continue to divide
- This uncontrolled cell division is what creates a cancer



Hematologic Cancers

- When cancer arises in a blood cell
- Can be acute vs. chronic
- Leukemia
- Lymphoma
- Plasma cell dyscrasias (e.g. multiple myeloma)





Leukemia

Acute

- Immature cells
- Need urgent treatment
- Typically curable

- Myeloid: Acute myeloid leukemia, APL
- Lymphoid: Acute lymphoblastic leukemia

Chronic

- Mature cells
- Sometimes do not even need treatment, just observation
- Typically incurable

- Myeloid: Chronic myeloid leukemia, MDS
- Lymphoid: Chronic lymphocytic leukemia

Acute Myeloid Leukemia (AML)

- Epidemiology
  - Relatively rare
  - Most common acute leukemia
  - ~20,000 new cases diagnosed each year
  - 75% of patients are older than 60 at diagnosis
- Risk Factors
  - Most patients do not have a risk factor, it's just bad luck
  - Radiation
  - Smoking
  - MDS
  - MPNs
  - Bone marrow failure syndromes and congenital disorders
    - Fanconi anemia
    - Down syndrome
    - Klinefelter syndrome
  - Chemotherapy
    - Accounts for 10-20% of new AML cases
    - Alkylating Agents: cyclophosphamide, cisplatin, carboplatin, mitomycin
    - Topoisomerase II inhibitors: Etoposide, doxorubicin, daunorubicin

AML

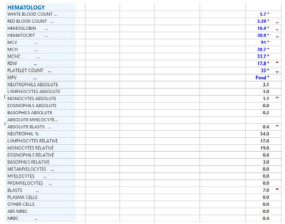
- Presentation
  - Symptoms
    - Shortness of breath
    - Fatigue
    - Bleeding/bruising
    - Headache or neurologic issues (concerning for leukostasis)
  - Physical findings
    - Pallor
    - Hepatosplenomegaly
    - Typically no lymphadenopathy (although this is possible)

AML

- Lab findings
  - Anemia
  - Thrombocytopenia
  - Leukocytosis
    - Due to increased blasts
  - Leukopenia
  - Peripheral blood smear can show circulating myeloblasts
  - Bone marrow biopsy to confirm diagnosis

AML Diagnosis

- Acute leukemia should be suspected in an ill appearing patient with new cytopenias
- CBC with differential is key!
- An elevated white count that is predominantly neutrophils is typically reactive
- Blasts should not be in the peripheral blood



AML Treatment

Younger, fit patients

- Aggressive induction chemotherapy
- 7+3 (3 days of anthracycline, 7 days of cytarabine)
- Typically done inpatient
- Can add midostaurin for patients with a FLT3 mutation
- Autologous transplant for higher risk patients
- Consolidation treatment for favorable risk patients and those waiting for donor

Older, frail patients

- We use an individual's fitness and comorbidities instead of chronological age
- Less intensive therapy
- Hypomethylating agents (decitabine, azacytidine) +/- venetoclax
- Targeted agents (IDH inhibitors)
- Palliative care

AML - Complications

- Neutropenic precautions
  - Neutropenic diet not necessary
  - Avoid anything per-rectum as this can cause translocation of bacteria in the blood stream
- Febrile neutropenia
  - Fever: ≥38.3°C (101°F) or a temperature of ≥38.0°C (100.4°F) sustained over a one-hour period
  - Neutropenia: absolute neutrophil count < 500 cells/microL
  - Medical emergency
  - Requires urgent antibiotics, typically cefepime +/- vancomycin

AML - Complications

- Infections
  - Bacterial- fluoroquinolone prophylaxis
  - Viral- acyclovir prophylaxis
  - Fungal- azole prophylaxis
- Tumor lysis syndrome
  - Elevated uric acid, phosphorus, potassium
  - Can cause kidney failure, arrythmias
  - Treated w/ rasburicase and allopurinol

AML - Complications

- Leukostasis
  - Blasts are "sticky" (wouldn't need to be as concerned if these are mature cells)
  - High risk when total WBC is > 50-100k
  - Medical emergency
  - Can cause respiratory or neurological issues
  - Treated w/ leukapharesis

Acute Lymphoblastic Leukemia(ALL)

- Epidemiology
  - Mostly seen in children
  - 75% of cases occur in children under the age of 6
  - Most common acute leukemia
  - Annual incidence worldwide is 1-5/100,000 population
- Risk Factors
  - More common in males
  - Incidence is 3x higher in White people than Black people
  - Hispanics are at highest risk, unclear why
  - Radiation
  - Down syndrome

ALL – Special considerations

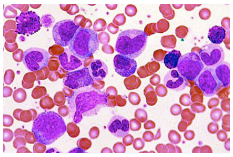
- Can arise in B cells (more common) and T cells
- Can have a mutation t(9,22); BCR-ABL1, also called the Philadelphia chromosome (seen in CML)
- Often spreads to the CNS
- Multiple treatment options, typically include an anthracycline, steroid, and vincristine along CNS prophylaxis

Chronic Myeloid Leukemia (CML)

- Myeloproliferative neoplasm due to the BCR-ABL1 fusion gene
- Epidemiology
  - Accounts for 15-20% of leukemias in adults
  - Median age at presentation is 50 yo
- Risk Factors
  - Radiation

CML - Diagnosis

- Peripheral blood
  - Leukocytosis (can be severe)
  - Neutrophilia
  - Basophilia
  - "Myelocyte bulge" – more myelocytes than metamyelocytes
- **BCR-ABL1 fusion gene**



CML - Disease Phases

- Chronic phase
  - Minimal symptoms if any
- Accelerated phase
  - 10-19% blasts in blood or bone marrow
  - Platelets < 100k not due to treatment
  - Worsening splenomegaly and leukocytosis
- Blast crisis
  - >20% blasts in blood or bone marrow

CML - Treatment

- Chronic phase
  - Treat with tyrosine kinase inhibitor targeting BCR-ABL1
    - Imatinib (1st generation)
    - Dsatainib, nilotinib, bosutinib (2nd generation)
  - Imatinib was one of the first "targeted agents" in oncology
  - Goal is to achieve remission and maintain disease control
  - Some patients who have a great response can come off the drug
- Accelerated phase and blast crisis
  - Typically use a TKI but can sometimes add in chemotherapy as well for blast crisis
- Younger patients will sometimes go to allogeneic transplant

Chronic Lymphocytic Leukemia (CLL)

- Chronic lymphoproliferative disorder leading to the production of monoclonal lymphocytes
- Epidemiology
  - Most common adult leukemia in Western countries
  - Accounts for 25-35% of leukemias in the U.S.
  - Male predominance
  - Median age at diagnosis is ~70 yo
- Risk Factors
  - More common in White Americans than African Americans or Asians
  - No known environmental risk factors
  - Possible genetic link

CLL - Diagnosis

- Symptoms
  - Fever
  - Night sweats
  - Weight loss
  - Fatigue
  - Bruising/bleeding
- Signs
  - Hepatosplenomegaly
  - **Lymphadenopathy**
- Labs
  - Lymphocytosis (>5000/microL)
    - This can be pronounced, but does typically not cause symptoms
  - Cytopenias
  - Hypogammaglobulinemia

CLL - Treatment

- Many patients can be observed, treatment is reserved for specific indications
- Indications for treatment
  - Progressive bone marrow failure w/ worsening anemia or thrombocytopenia
  - Massive or symptomatic splenomegaly
  - Massive or symptomatic lymphadenopathy
  - Constitutional symptoms
  - Progressive lymphocytosis w/ a fast doubling time

CLL - Treatment

- Many first line options
- Use risk stratification and fitness/age of the patient to guide management
- Patients w/ Del(17p) have high risk disease
  - Ibrutinib or acalabrutinib
  - Ibrutinib + rituximab
  - Venetoclax + obinutuzumab
- Standard risk patients
  - Ibrutinib alone is good for older patients and those who are less fit
  - Ibrutinib + rituximab
  - Venetoclax + obinutuzumab
  - BR

Ibrutinib

- Bruton tyrosine kinase (BTK) inhibitor
  - Inhibition of BTK leads to decreased proliferation and survival of the CLL B-lymphocytes
- Can cause atrial fibrillation
- Acalabrutinib
  - Newer BTK inhibitor with less Afib risk
- Can cause an initial increase in the lymphocyte count

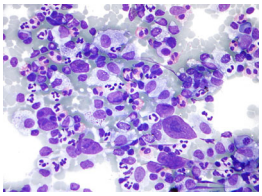
Lymphoma

Aggressive
- Immature cells
- Need urgent treatment
- Typically curable
- B cells: DLBCL, Burkitt lymphoma
- T cells: Peripheral T cell lymphoma
- Hodgkin lymphoma

Less aggressive
- Mature cells
- Sometimes do not even need treatment, just observation
- Typically incurable
- B cells: MZL, follicular, SLL

Hodgkin Lymphoma

- Treated very differently from "Non-Hodgkin lymphoma" which is a very broad term
- Lymphoid neoplasm involving Reed-Sternberg cells interspersed amongst non-malignant inflammatory cells
- Nodular sclerosis subtype is the most common (70%)
- Nodular lymphocyte predominant Hodgkin lymphoma is very different and generally not aggressive



Hodgkin Lymphoma

- Epidemiology
  - Bimodal age distribution
  - Peak in young adulthood and in older adults
  - Accounts for 0.6% of all cancers in Western world
  - 10% of all lymphomas
- Risk factors
  - EBV infection
  - Obesity
  - Immunosuppression
  - Familial risk

Hodgkin Lymphoma - Diagnosis

- Blood work and PET scan first
- Excisional biopsy if possible of an FDG avid lymph node
- Presentation
  - Lymphadenopathy
  - B symptoms (fever, night sweats, weight loss)
  - Cytopenias
  - Organ dysfunction

Hodgkin Lymphoma - Treatment

- Most patients will be cured
- Need to minimize treatment related toxicities
- Stage I-II
  - Chemotherapy +/- radiation
- Stage III-IV
  - Chemotherapy

ABVD

- Doxorubicin
  - Cardiotoxicity, need ECHO prior to treating
  - Vesicant, requires mediport
  - Can turn bodily fluids red
  - Risk of secondary malignancies
- Bleomycin
  - Rare but life threatening pulmonary toxicity
- Vinblastine
- Dacarbazine

- Very low risk of febrile neutropenia
- Do not use G-CSF as a results
- Given every 2 weeks
- Can often drop bleomycin after C2 if interim PET scan shows a good response

Non-Hodgkin Lymphoma (NHL)

- This is a very broad, nonspecific term
- Diverse group of malignancies, can be indolent or very aggressive
- Can involve mature B cells, mature T cells, B cell progenitors, T cell progenitors, and rarely NK cells

Diffuse Large B cell Lymphoma (DLBCL)

- Most common subtype of NHL (25% of all NHL cases)
- Aggressive
- Can present as lymphadenopathy or extranodal mass
- B symptoms are common
- 60% of patients will have advanced stage disease at diagnosis
- Use cytogenetics to determine which patients need more aggressive treatment (double hit and double expressors)
- R-CHOP vs R-EPOCH

Rituximab

- Anti-CD20 monoclonal antibody
- Commonly used for B cell malignancies which express CD20
- Can lead to hepatitis reactivation so need to check serologies prior to administration
- Can cause a severe infusion reaction

Burkitt Lymphoma

- Extremely aggressive B cell NHL
- Involves translocation of the MYC oncogene
- Requires aggressive chemoimmunotherapy
- Rituximab usually incorporated in treatment regimen
- R-CODOX-M/IVAC vs. R-EPOCH
- High risk for tumor lysis

Follicular Lymphoma

- Second most common type of NHL
- Involves mature B-cells
- Typically very indolent with excellent prognosis
- For the most part, incurable but there is debate about this
- Can observe if not symptomatic
- High grade follicular lymphoma is treated like DLBCL
- Can use radiation, rituximab alone, or bendamustine + rituximab amongst others

Multiple Myeloma (MM)

- Plasma cells originate from B lymphocytes and produce antibodies
- MM is a cancer of these plasma cells
- Epidemiology
  - 1-2% of all cancers
  - Accounts for ~17% of hematologic malignancies
  - More common in men than women
  - More common in African Americans
  - Affects older adults (median age at diagnosis is 65-74 yo)
- Risk factors
  - Increased BMI
  - Agent Orange exposure
  - MGUS

MM - Diagnosis

- Presentation
  - Anemia
  - Bone pain
  - Renal dysfunction
  - Fatigue
  - Hypercalcemia
  - Weight loss
- **CRAB** (Calcium, renal dysfunction, anemia, bone lesions)
- Labs
  - Serum protein electrophoresis
    - Helps detect a monoclonal protein which myeloma plasma cell produce
    - M spike
  - Free light chains
    - Kappa vs lambda
  - Bone marrow biopsy
    - Need ≥ 10% clonal plasma cells
- Imaging
  - PET/CT/X rays to look for bone lesions

MM - Treatment

- Use labs and cytogenetics to risk stratify patients
- Need to know if the patient is a candidate for autologous HCT
- High risk, HCT eligible
  - 4 cycles of bortezomib, lenalidomide, dexamethasone (VRd) +/- daratumumab
  - HCT
  - Proteasome inhibitor maintenance
  - HCT is not curative but prolongs surviva
- If not eligible for transplant, can do 8-12 cycles of VRd
- Standard risk, HCT eligible
  - 4 cycles VRd
  - HCT
  - Lenalidomide maintenance

Future Directions

- CAR-T therapy
- Targeted agents
- Immunotherapy