Introduction to Malignant Hematology

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1

Disclosures

- No relevant financial disclosures

2

Outline

- Acute Leukemias
  - Acute Myeloid Leukemia
  - Acute Lymphoid Leukemia
- Chronic Leukemias
  - Chronic Myeloid Leukemia
  - Chronic Lymphoid Leukemia
- Lymphoma
  - Hodgkin
  - Non Hodgkin
- Myelodysplastic Syndrome
- Multiple Myeloma
- Myeloproliferative Neoplasms

3

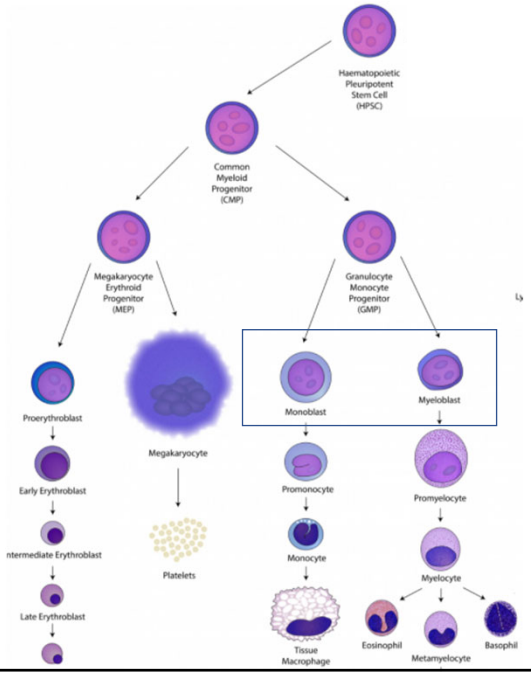
Acute Leukemia Presentation/Initial Management

- Clinical presentation: Bleeding (thrombocytopenia, DIC), Fever (neutropenia), fatigue (anemia), low blood counts on CBC, dyspnea or headache (leukostasis), AKI, hyperkalemia (tumor lysis syndrome)
- May have blasts on CBC diff
- Acute interventions
  - Transfusions (Goal plt > 10, hgb > 7, correct coagulopathy)
  - Evaluation of life threatening bleeding (CT head if any headache)
  - Tumor Lysis Syndrome (uric acid, phos, potassium, calcium, Cr) → Rasburicase, Allopurinol
  - Infectious Evaluation (empiric antibiotics for any neutropenic fever)
  - Evaluation for leukostasis (clinical evaluation, CXR) and leukapheresis if suspected leukostasis
- DX: ≥20% blasts in peripheral blood or bone marrow BX

4

Acute Myeloid Leukemia

- Median age of diagnosis 68
- 20,000 new cases per year (1% of all cancers)
- Risk factors: Older age, smoking, benzene, prior chemotherapy or radiation, genetic syndromes (bone marrow failure [Fanconi anemia, Bloom Syndrome, Dyskeratosis Congenita, etc.] or chromosomal disorders [Down Syndrome])



5

Principles of Treatment of AML

- Prompt identification of Acute Promyelocytic Leukemia (flow cytometry, FISH for PML-RARa)
  - Risk for DIC/Life threatening bleeding. Start differentiation therapy empirically (ATRA) if suspected APL.
- Leucoreduction with Hydrea while awaiting diagnostic testing
- Disease risk good risk, int risk, adverse risk
  - Good risk → chemotherapy only (~70-80% long term survival)
  - Int risk → chemotherapy or alloHCT (~50% long term survival with chemo, 70% with alloHCT in CR1)
  - Adverse risk → alloHCT in CR1 (~20% long term survival with chemo, 40-50% with alloHCT in CR1)
- Fit vs Unfit, Age (>75), disease risk
  - Intensive induction vs. Less intensive therapy (Ven/HMA combos)
  - Transplant vs. no transplant

6

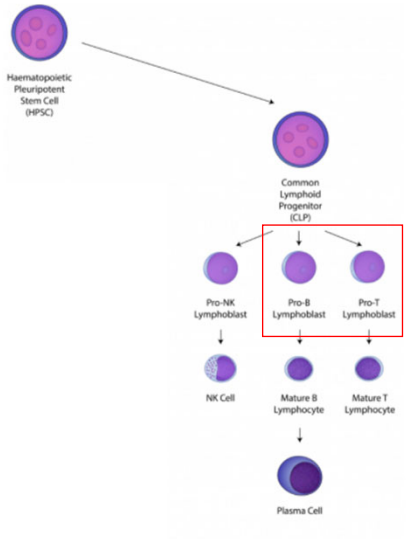
Common AML Treatments

Chemotherapy	Mechanism	Side effects
Daunorubicin/Idarubucin	Cytotoxic	Cardiotoxicity, myelosuppression
Cytarabine	Cytotoxic	Myelosuppression, rash High dose (>1g/m2): conjunctivitis, neurotoxicity
Cyclophosphamide	Cytotoxic	Myelosuppression, hemorrhagic cystitis, mucositis, hepatotoxicity, alopecia
Midostaurin/Gilteritinib	FLT3 inhibitor	QT prolongation, diarrhea, rash
Venetoclax	BCL2 inhibitor	Myelosuppression, nausea, fatigue
Azacitidine/Decitabine	Hypomethylating Agents	Myelosuppression, fatigue
Ivosidenib	IDH1 inhibitor	QT prolongation, differentiation syndrome
Enasidenib	IDH2 inhibitor	QT prolongation, differentiation syndrome
Glasdegib	Smoothened hedgehog inhibitor	QT prolongation, fatigue, diarrhea
Gemtuzumab	CD33 mAB	Hepatotoxicity (Venoocclusive disease), myelosuppression

7

Acute Lymphoblastic Leukemia

- Median Age: bimodal (children < 5 years + adults > 50)
  - 80% of deaths from ALL in adults
- 6600 new cases per year (0.5% of new cancers)
- 2/3 B-Cell, 1/3 T-Cell
- Risk factors: Benzene, some viruses (HTLV-1, EBV), congenital (Down syndrome, Fanconi anemia, Klinefelter)



8

Principles of Treatment of ALL

- FISH for PH chromosome (9:22)
  - Add TKI to chemotherapy backbone
- Need CNS prophylaxis due to high rate of CNS involvement/relapse
  - IT chemo, high dose MTX and Cytarabine
- Prolonged Treatment course with combination chemo only in induction, consolidation, maintenance phases (2-3 years)
- AlloHCT is often indicated for high risk disease in CR1, or any CR2
- Check BCR-ABL- if positive, add TKI (Imatinib, Dasatinib)

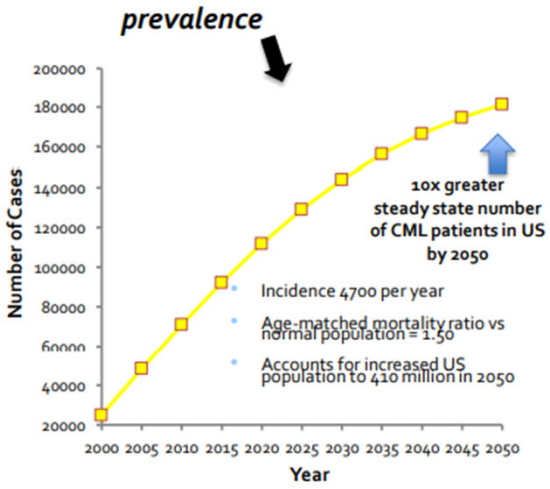
9

Common ALL Treatments

Chemotherapy	Mechanism	Side effects
Doxorubicin	Cytotoxic	Cardiotoxicity, myelosuppression
Vincristine	Cytotoxic	Neuropathy, Constipation/Ileus
Steroids	Lymphotoxic	Hyperglycemia, hypertension, Opportunistic Infection (PJP)
Cyclophosphamide	Cytotoxic	Myelosuppression, hemorrhagic cystitis, mucositis, hepatotoxicity
Asparaginase	Depletes Asparagine	Hepatotoxicity, Pancreatitis, Coagulopathy/DIC, Thrombosis
Intrathecal Chemotherapy	Cytotoxic	Headache, nausea, rare neurotoxicity
Blinatumomab	CD20xCD3 BiTE	Cytokine Release Syndrome, neurotoxicity
Inotuzumab	CD22 mAB	
Imatinib, Dasatinib, Ponatinib	Tyrosine Kinase Inhibitors (PH+)	Imatinib- edema, GI toxicity, rash Dasatinib- effusions, thrombocytopenia, plt dysfunction Ponatinib- vascular thromboses

10

Chronic Myeloid Leukemia



15-20% of leukemias in adults

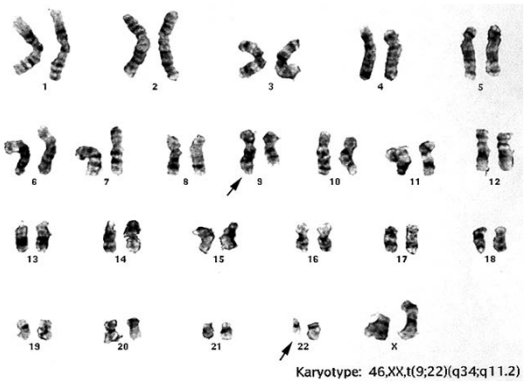
T(9;22) (Philadelphia Chromosome)

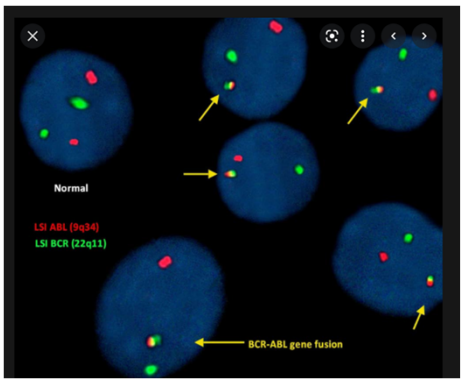
Median age at presentation ~50

Clinical presentation
- Asymptomatic (common)
- Fatigue, weight loss, sweats, abdominal fullness, LUQ pain, sternal pain

Exam and labs
- Splenomegaly
- Leukocytosis, Anemia, thrombocytosis

11

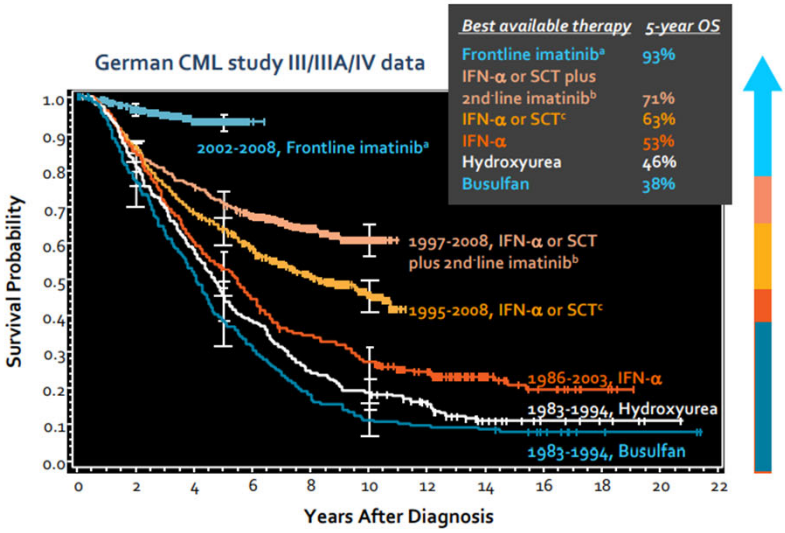




CG/FISH/PCR for BCR-ABL is diagnostic

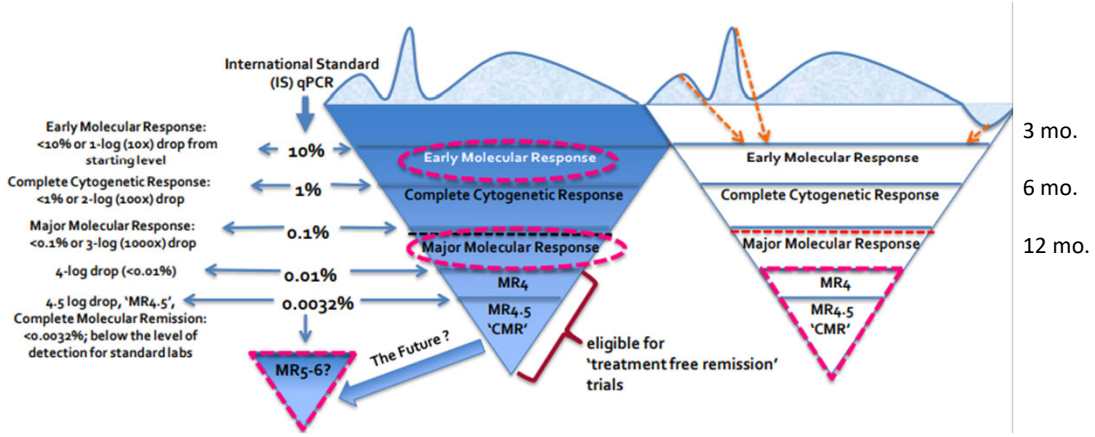
*Atypical CML that is Ph-negative exists (+8, 17q abnl)

12



13

CML Response Milestones



14

Treatment- TKIs

- Imatinib (Gleevec)
- Dasatinib (Sprycel)
- Nilotinib (Tasigna)
- Ponatinib (Iclusig)
- Ascimitinib (Scemblix)

Issue	Imatinib	Nilotinib	Dasatinib	Bosutinib	Ponatinib
Dosing	QD/BID, with food	BID, without food (>h)	QD, w/ or w/o food	QD, with food	QD, w/ or w/o food
Long term safety	Most extensive	Extensive; Emerging toxicity	Extensive; Emerging toxicity	Extensive, No emerging toxicity	More limited but increasing; Emerging toxicity
Heme toxicity	intermediate	least	Most severe; ASA-like effect; lymphocytosis	~dasatinb in 2nd, 3rd line; ~nilotinib in 1st line	↑thrombocytopenia ASA-like effect
Non-Heme toxicity	Edema, GI effects, ↓Phos	↑lipase, ↑bili, ↑chol, ↑glu Black box: QT prolongation; screening req'd	Pleural / pericardial effusions	Diarrhea; transaminitis	↑lipase, pancreatitis; rash; hypertension; Black box: vascular occlusion, heart failure, and hepatotoxicity
Emerging toxicities	early question re: CHF; ?late renal effects	Vascular events (ICVE, IHD, PAD)	PAH (pulmonary arterial hypertension)	? Mild renal effects	Vascular events (ICVE, IHD, PAD, VTE)

15

Principles of CML Treatment

- Accelerated phase: BM or PB blasts 5-10% → 2nd/3rd gen TKIs
- Blast phase: BM or PB blasts > 20% →Treated like acute leukemia
  - Usually Myeloid blast phase, but can lineage switch to lymphoid blast phase (Ph+)
  - Goal to cytoreduce with chemotherapy + TKI, then consider allogeneic hematopoietic stem cell transplantation
- If TKI stops working, consider sending TKI mutational analysis (T315I)
- Some patients are candidates for TKI discontinuation after achieving prolonged molecular remission (~15%)
- Financial Toxicity (TKIS are $$$ for indefinite duration)

16

Chronic Lymphocytic Leukemia/Small Lymphocytic Leukemia

- Most common hematologic malignancy (prevalence 200K cases yearly, 15K new cases per year)
- CLL → in blood, SLL → in lymph nodes
- Median age at dx 72
- Unknown etiology, ~10% have family history of lymphoma
- Generally indolent and treatable, but not considered curable
- Survival can range from a few months to 20+ years (median ~10 years)

17

CLL Diagnosis/Prognosis

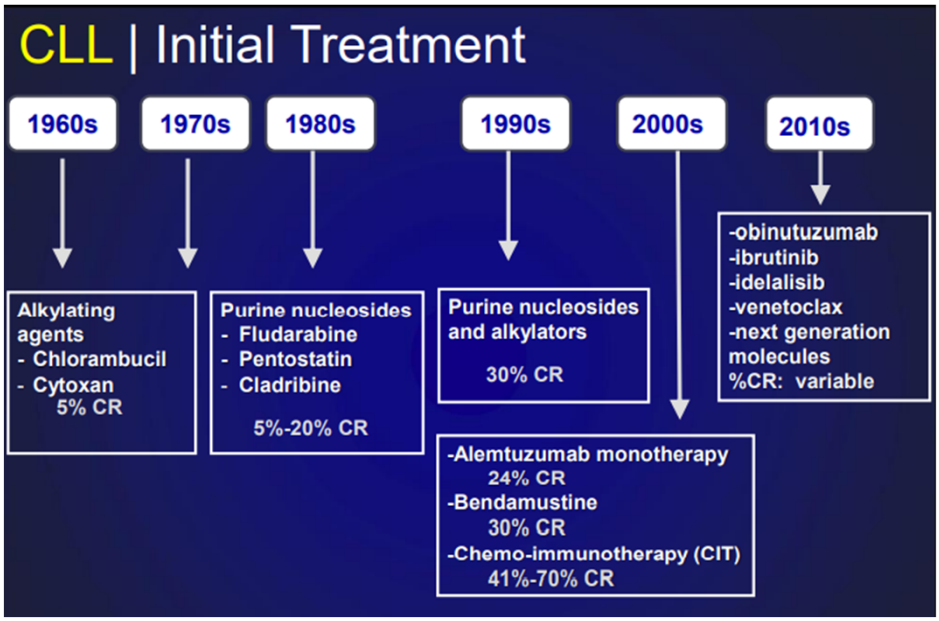
- Bone marrow biopsy is not needed for diagnosis
- May be diagnosed on lymph node biopsy (SLL)
- FISH testing on blood/LN
  - 17p deletion (TP53 mutation), del11q, and complex cytogenetics are higher risk
  - IGHV unmutated, ZAP70+, CD38+ are unfavorable
- PET or CT scan if clinical suspicion for LAD/splenomegaly

18

CLL Clinical Manifestations

- Cytopenias
  - May be autoimmune (AIHA, ITP)
- Infection
  - Immunoglobulins may be low
- B-symptoms and symptoms related to LAD/Splenomegaly
  - Wt loss, fatigue, night sweats, early satiety

19



20

Principles of Treatment for CLL

- Many early stage CLL/SLL patients can be monitored off treatment
- Most patients in modern era will have first line treatment with Ibrutinib or Venetoclax + Obinatuzumab
- Leukocytosis with lymphocytosis generally is not a reason to treat (lymphocytes do not cause leukostasis)
- CLL can transformed into more aggressive NHL (Richter's transformation), biopsies may be necessary
- AlloHCT is rarely indicated now due to less toxic treatments

21

Lymphomas

- Symptoms
  - Painless adenopathy
  - Hepatosplenomegaly
  - Fevers, night sweats, weight loss
  - Pain with organ infiltration (bone)
  - Fatigue
  - Hypercalcemia
  - Thrombosis
- Hodgkin vs. Non-Hodgkin

22

Lymphoma Workup

- PET scan (CT + metabolic uptake)
- CBC, BMP, LFTs, uric acid, phosphorus, LDH
- Hepatitis and HIV testing
- Bone marrow biopsy (if it changes stage or cytopenias)
- CSF analysis (high grade lymphomas, testicular/renal/breast involvement)

23

Non Hodgkin Lymphomas

- Derived from mature B and T-cells at varying stages of development
- Aggressive
  - Diffuse Large B-cell lymphoma (curable)
  - Mantle Cell Lymphoma
  - Burkitt Lymphoma (curable)
  - Peripheral T-cell Lymphoma (curable)
  - CNS Lymphoma (curable)
- Indolent
  - Follicular Lymphoma
  - Marginal Zone Lymphoma
  - Small Lymphocytic Lymphoma

24

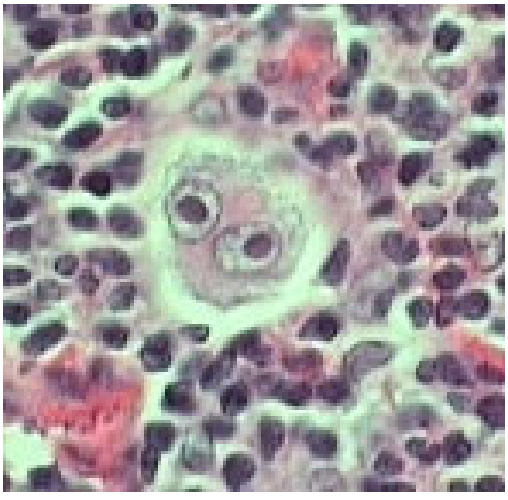
Principles of Treatment for NHL

- Aggressive, symptomatic lymphomas need quick intervention with chemotherapy
- High response rates with combination chemotherapies + steroids
- B-cell lymphomas → Rituxan added to chemo backbone
- T-cell lymphomas → ALK+ is a favorable subgroup, others have worse prognosis compared to B-cell lymphomas
- Auto-Transplant or CAR-T at relapse

25

Hodgkin Lymphoma

- B- cell Origin
- Reed Sternberg cell
- Young Adults (18-40 year olds) and older adults (60s-70s)
- 90% Classical Hodgkin, 10% other subtypes
- Symptoms
  - Neck and Mediastinal mass
  - B-symptoms
  - Pruritis



26

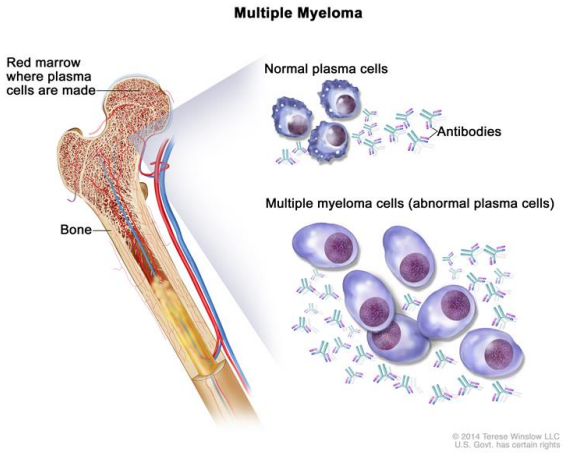
Principles of Treatment for Hodgkin

- High cure rate (~80% with chemotherapy)
  - ABVD or A-AVD (Brentuximab+AVD)
- Brentuximab (CD30 mAB) and Nivolumab (immune checkpoint inhibitor) are novel therapies used in upfront and relapsed setting
- With ABVD, neutropenia is common but neutropenic fever less frequent, so chemotherapy often proceeds despite neutropenia (high cure rates)
- AutoHCT at relapse

27

Multiple Myeloma

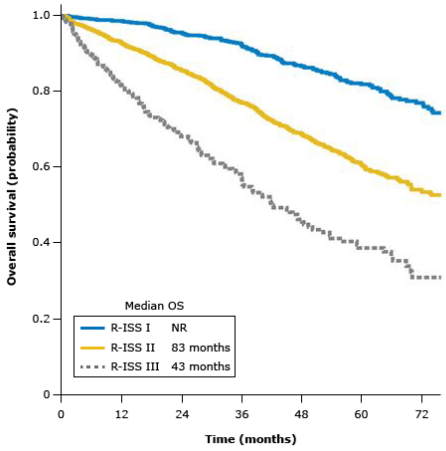
- Plasma cell disorder
- 34K cases per year
- Diagnosed by 60% marrow involvement by clonal plasma cells, or 10% clonal plasma cells + CRAB criteria
- C- hypercalcemia
- R- Renal injury
- A- Anemia
- B- Bone lesions (lytic)



28

Myeloma

- Prognosis: ~55% survival at 5 years, 30% survival at 10 years
- Survival is improving due to effectiveness of novel therapies
- R-ISS is staging system for prognosis (albumin, beta-2-macroglobulin, high risk abnormalities by FISH [del17p, t(4;14), t(14;16)]



Palumbo A, Avet-Loiseau H, Oliva S, et al. Revised International Staging System for Multiple Myeloma: A Report From International Myeloma Working Group. J Clin Oncol 2015; 33(26):2863-9.

29

Myeloma Workup

- Bone marrow biopsy (%plasma cells, FISH testing)
- CT, PET scan, or whole body MRI (bone involvement)
- SPEP, free light chains (kappa, lambda), serum and urine immunofixation, 24-hour urine protein electrophoresis
- Creatinine, calcium, LDH, albumin, beta-2-microglobulin

30

Myeloma Treatments

Chemotherapy	Mechanism	Side effects
Bortezomib (Velcade)	Proteasome Inhibitor	Neuropathy, Thrombocytopenia
Carfilzomib	Proteasome Inhibitor (2nd generation)	Neuropathy, Cardiotoxicity
Lenalidomide (Revlamid)	Immunomodulator	Thomboses, birth defects, diarrhea, secondary malignancies
Pomalidomide	Immunomodulator (2nd generation)	Thromboses, myelosuppression, rash, hepatotoxicity
Daratumomab	CD38 mAB	Infusion reaction, nausea, fatigue Interferes with T&S
Elotuzumab	SLAMF7 antibody	Infection, fatigue, neuropathy
Belantamab mafodotin	BCMA mAB	Keratopathy, infusion reactions
AutoTX (Melphalan)	Cytotoxic	Fatigue, myelosuppression, alopecia, secondary malignancies

31

Myelodysplastic Syndrome

- Myeloid malignancy resulting in bone marrow failure
- Low, Intermediate, or High risk based on blood counts, %blasts in blood, cytogenetics
- Low risk → can be watched, supportive care with Epo or G-CSF
- Int/High Risk → Hypomethylating Agent or AlloHCT
- Risk of transformation to AML and severe cytopenias requiring transfusional support
- Curable with alloHCT

32

Other Myeloproliferative Neoplasms

- Polycythemia Vera, Essential Thrombocythemia, Myelofibrosis
- Present with elevated blood counts, splenomegaly, thrombosis, fatigue, night sweast, pruritis, fever, weight loss
- JAK2 mutation (most common), also CALR and MPL mutations
- P. Vera → Elevated Hgb/Hct. Manage with therapeutic phlebotomy.
- ET → Hydrea to reduce platelet count to <400, ASA
- Myelofibrosis → Hydrea or Ruxolitinib for symptoms/cytoreduction, alloHCT for cure in high risk

33

Questions?

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34