HEMATOLOGIC MALIGNANCIES

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- This speaker has been asked to disclose to the audience any involvement with industry or other organizations that may potentially influence the presentation of any educational material

- Receiving evaluations is critical to the accreditation process. After the program, please provide feedback at https://survey.dal.ca/opinion/s?s=45474

DISCLOSURES

- I was a consultant at Adboard meetings with:
  - Amgen
  - Celgene
  - Janssen Pharmaceutical Companies of Johnson & Johnson
  - Jazz Pharmaceuticals
  - Novartis Pharmaceuticals Canada Inc.
  - Sanofi Genzyme
- I am currently participating in or have participated in multiple industry-sponsored clinical trials within the past two years

OBJECTIVES

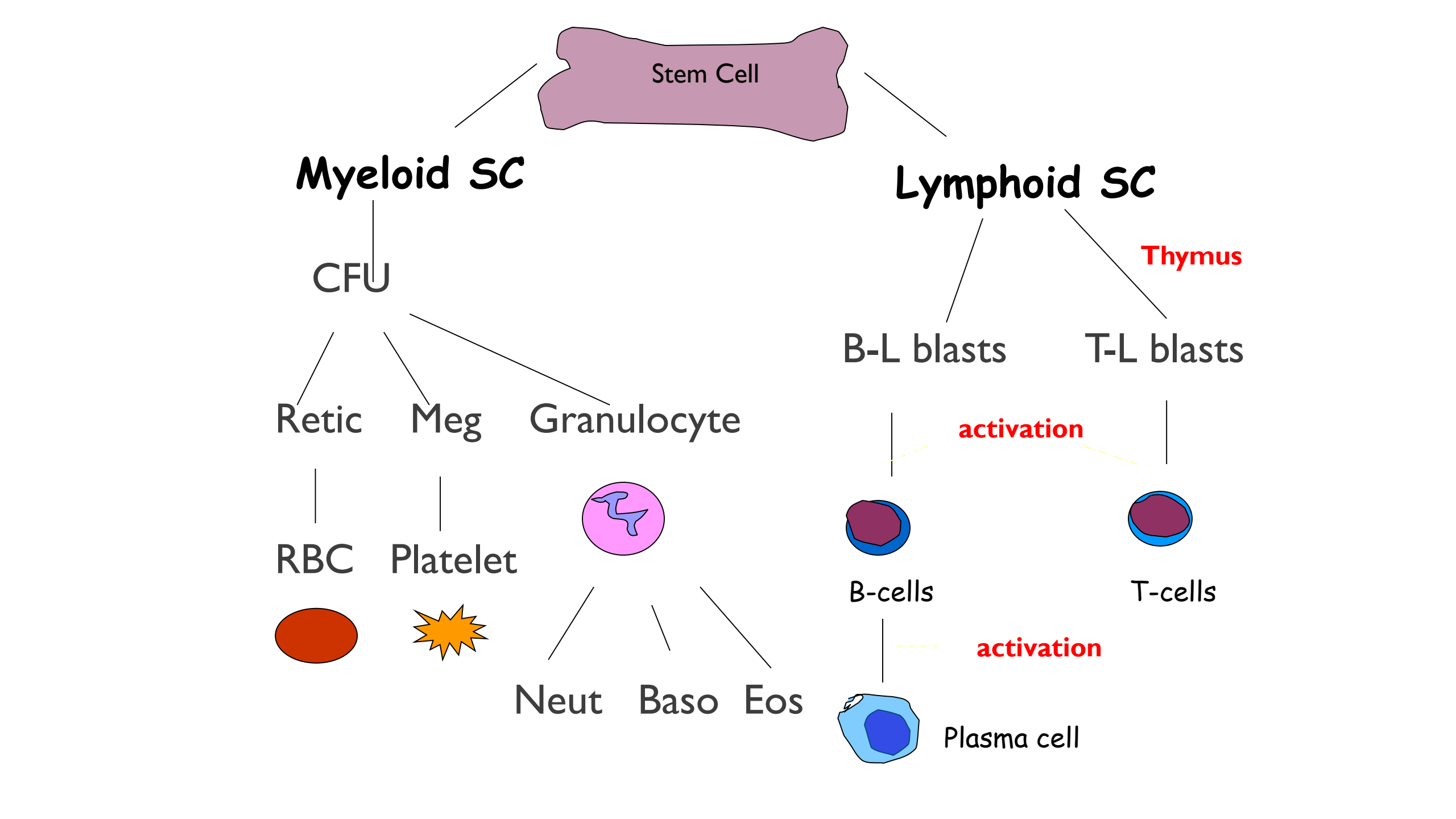
- Learn to recognize signs of hematologic malignancy
- Know when to refer to a Hematologist
- When is an urgent referral appropriate?
  - Review some hematologic emergencies
- Learn about some useful diagnostic or staging investigations

WE WILL REVIEW

- Lymphoma
- Myeloma
- Acute leukemia (AML, ALL, Burkitt)
- Chronic lymphocytic leukemia (CLL)
- Chronic myeloid leukemia (CML)
- Myelodysplastic syndrome (MDS)
- Myeloproliferative syndrome (MPD)

HEMATOLOGIC MALIGNANCY

- Proliferation of clonal cells originating from the bone marrow
  - Cells in the lymph nodes originate from the bone marrow


Stem Cell
Myeloid SC
Lymphoid SC
Thymus
CFU
B-L blasts
T-L blasts
Retic
Meg
Granulocyte
activation
RBC
Platelet
B-cells
T-cells
activation
Neut
Baso
Eos
Plasma cell

HEMATOLOGIC MALIGNANCY

- Proliferation of clonal cells originating from the bone marrow
  - Cells in the lymph nodes originate from the bone marrow

- All a treatable and some are potentially curable
  - Treatment involves supportive care +/- chemotherapy, radiation, rarely surgery
  - Therefore it is worthwhile to refer all cases to a Hematologist

HEMATOLOGIST'S TOOLKIT

- Bloodwork
  - Complete blood count (CBC)
  - Creatinine
  - Calcium and albumin
  - Lactate dehydrogenase (LD)
  - CT scan neck/chest/abdomen/pelvis or PET/CT scan
  - Bone marrow and/or lymph node biopsy
    - Fine needle aspirate, cytology usually not enough for diagnosis

CASE 1

- 59 year old male presents with back pain gradually worsening over 3 months
- He also complains of 20 pounds unexplained weight loss but no fevers or night sweats
- You find a 3 cm left axillary lymph node on physical examination
- You order a CT scan chest/abdomen/pelvis and refer him to a surgeon for lymph node biopsy

- He presents to the ER with severe back pain, unable to walk, while awaiting results of the biopsy

LYMPHOMA

- Incidence 20.8/100,000
  - Sixth most common cancer in Canada

- Presentation
  - Lymphadenopathy and hepatosplenomegaly
  - B symptoms (unexplained fever, unexpected weight loss >10% baseline, drenching night sweats)
  - Extranodal involvement
  - Metabolic

Age-standardized incidence rate from Canadian Cancer Statistics 2017

COMPLICATIONS

	Complication	Mechanism
Lymphadenopathy	SVC syndrome, Tracheal obstruction, Hydronephrosis, Spinal cord compression, Intestinal obstruction	Compression from nodal mass
Extranodal involvement	CNS symptoms Cytopenias Liver, lung, heart failure…	Organ dysfunction from tumour infiltration
Metabolic	Tumour lysis syndrome Hypercalcemia of malignancy Hyperviscosity syndrome Cancer-associated thrombosis	

CLASSIFICATION

Type	Aggressiveness	Common examples
Hodgkins		
Non-Hodgkin, B-cell	Indolent	Follicular lymphoma Marginal zone or MALT lymphoma Waldenstrom's lymphoma Small lymphocytic lymphoma
	Aggressive	Diffuse large B-cell lymphoma Mantle cell lymphoma Double-hit lymphoma
	Highly aggressive	Burkitt's lymphoma Acute lymphoblastic lymphoma
Non-Hodgkin, T-cell	Indolent	Mycosis fungoides
	Aggressive	Anaplastic large cell lymphoma Peripheral T-cell lymphoma
PTLD		

DIAGNOSIS

- Lymph node biopsy (or other tissue)
- Surgeon or interventional radiology
- Ask for Lymphoma protocol
- Most lymphomas reviewed by Hematopathology in Halifax
- Turn-around time 2 weeks (3 weeks if biopsy is done outside Halifax)

STAGING

- CT scan neck, chest, abdomen and pelvis
  - +/- bone marrow biopsy, PET/CT scan, MRI brain and/or spine, lumbar puncture

- Modified Ann Arbor staging system

Stage	
I	Single lymph node region
II	2 or more lymph node regions on same side of diaphragm
III	Lymph node regions on both sides of diaphragm
IV	Diffuse involvement of 1 or more extranodal organs including bone marrow
A = no B symptoms, B = B symptoms, E = single adjacent extranodal site, X = bulky disease	

NATURAL HISTORY

Hodgkin lymphoma	Follicular lymphoma	Diffuse large B cell lymphoma
Onset months to a year Moves from one lymph node to the next Highly curable with chemotherapy +/- radiation	Onset over years Waxing and waning course Not curable, but can live for years with treatment Up to10% transform to DLBCL	Onset over months Aggressive course, often widespread disease Potential cure with chemotherapy
ABVD	Rituxan and bendamustine	R-CHOP

CASE 1 CONTINUED

- MRI thoracic spine performed

SPINAL CORD COMPRESSION

- **Back pain in the setting of cancer**

- Etiology:
  - Cancer (breast, lung, prostate, renal, myeloma)
  - T-spine 70%, L-spine 20%, C-spine 10%
  - Abscess, hematoma, herniated disc...

PRESENTATION

- Early: back pain for weeks to months
  - Increases with movement, lying, cough, sneeze
- Intermediate: weakness ± sensory loss
  - Radiculopathy at level of compression with paresthesia in dermatome, muscle weakness
  - Myelopathy below level of compression with bilateral weakness and sensory loss
- Late: urinary retention, constipation

DIAGNOSIS

- X-ray spine
  - Not helpful
- MRI spine with gadolinium enhancement
  - Increased intensity T2 weighted images
- CT myelogram
  - Complication acute decompensation

TREATMENT

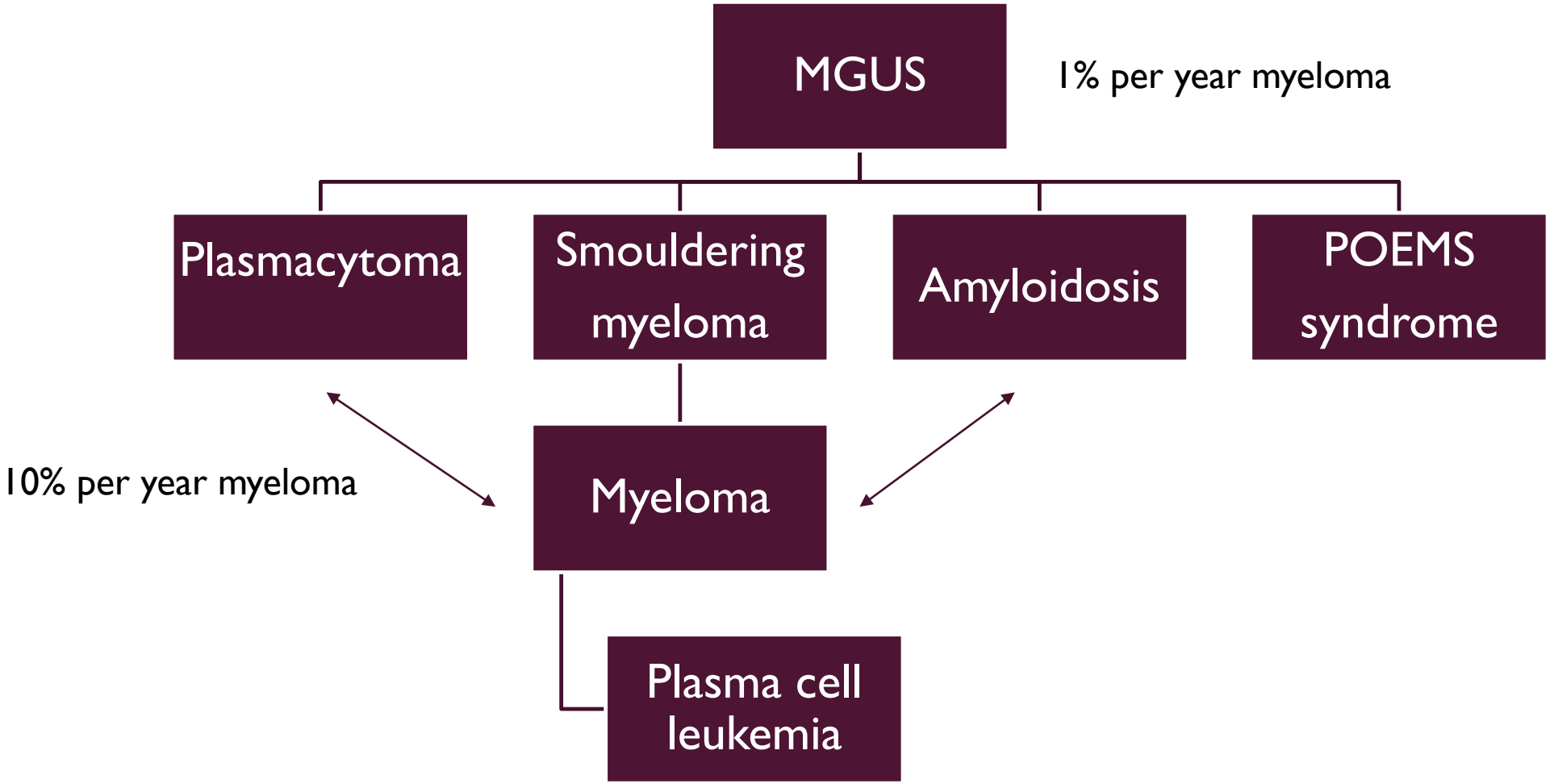
- **Must treat within 24-48 hours if symptoms severe**
- Dexamethasone 10 mg IV, then 4 mg q6h
- Neurosurgery consult
  - Diagnostic, stabilize spine
  - Severe rapid onset symptoms, radiation contra-indicated or failed, not cancer
- Radiation Oncology consult

Status prior to radiation	Ambulatory after treatment
Ambulating	98%
Not ambulating	60%
Paraplegic	11%

CASE 2

- 65 y o female with increasing fatigue for 6 months
- No fevers, night sweats or weight loss
- 1 week history of nausea, and generalized weakness
- CBC shows hemoglobin 85, WBC and platelet counts normal
- Calcium 2.4, albumin 20, and creatinine 600
- You order a serum protein electrophoresis (takes 3 weeks for results)

SPECTRUM OF PLASMA CELL DYSCRASIAS

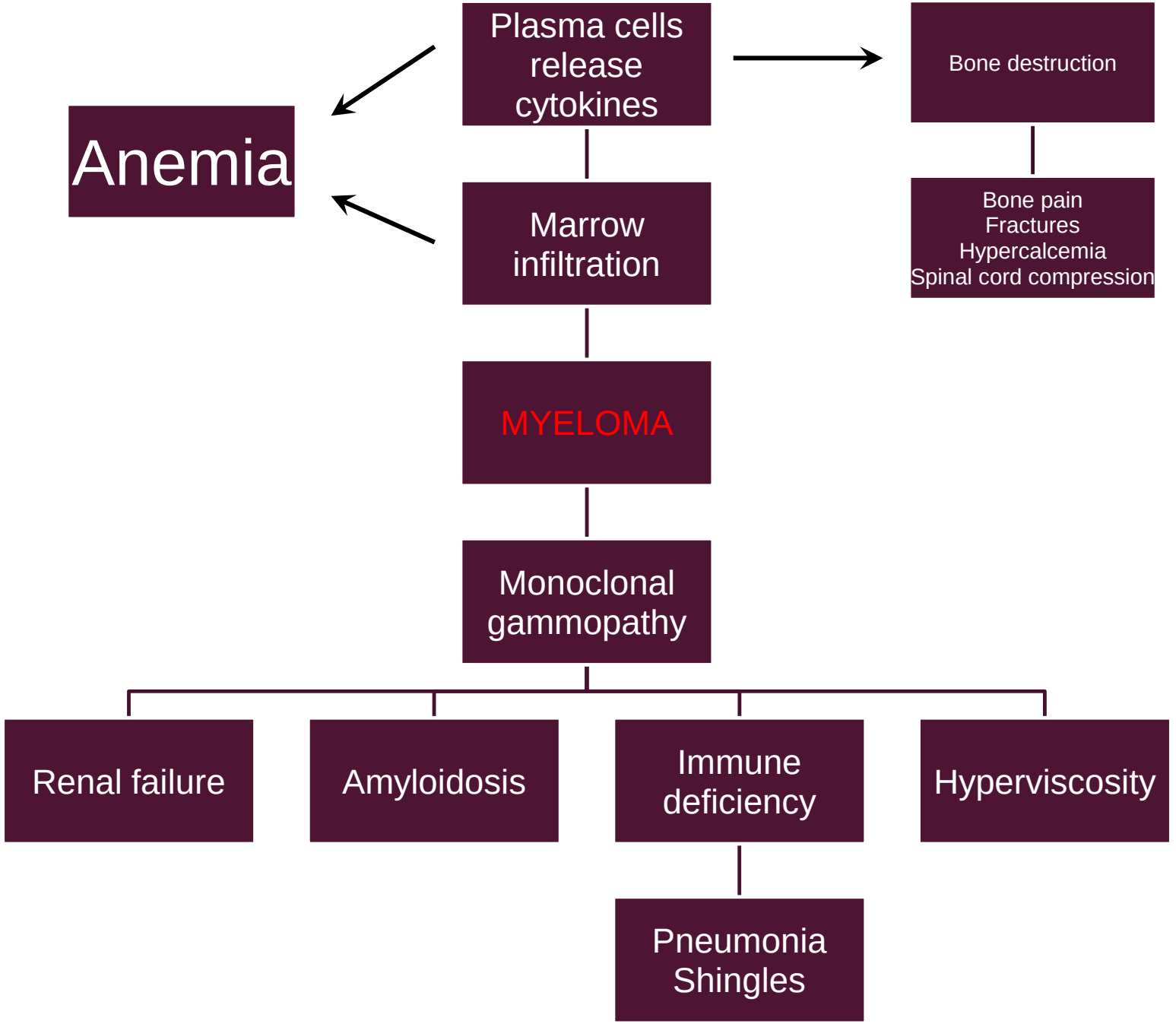


MYELOMA

- Incidence 7.1/100,000
  - Sixteenth most common cancer in Canada

- Presentation
  - HyperCalcemia
  - Renal failure
  - Anemia
  - Bone fracture or painful lytic bone lesions

Age-standardized incidence rate from Canadian Cancer Statistics 2017


Plasma cells release cytokines
Bone destruction
Anemia
Marrow infiltration
Bone pain
Fractures
Hypercalcemia
Spinal cord compression
MYELOMA
Monoclonal gammopathy
Renal failure
Amyloidosis
Immune deficiency
Hyperviscosity
Pneumonia
Shingles

DIAGNOSIS

- Find a MONOCLONAL GAMMOPATHY
  - Quantitative immunoglobulins
  - Serum protein electrophoresis
  - Immunoelectrophoresis
  - Serum free light chains
  - (24 hour urine total protein for amyloidosis)
- Bone marrow aspirate and biopsy
- +/- plasmacytoma biopsy

STAGING

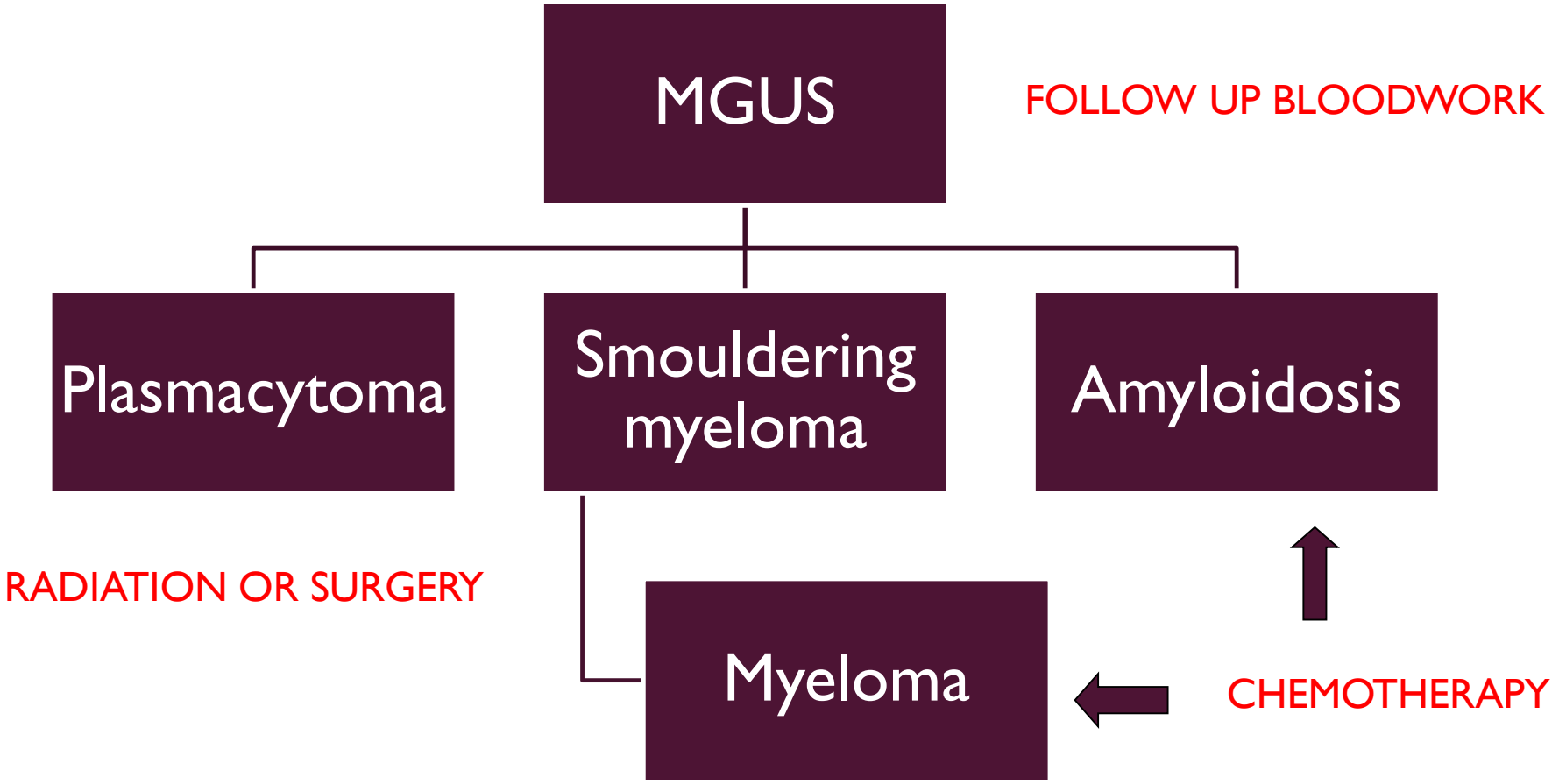
Stage	$\beta_2$microglobulin	Albumin	Median survival (months)
I	<	≥35 G/L	62
II	In between stage I and III		44
III	≥		29

ISS

	I (all criteria)	II	III (any criteria)
Hemoglobin	> 100 G/L		< 85 G/L
IgG	< 50 G/L		> 70 G/L
IgA	< 30 G/L		> 50 G/L
Calcium	Normal		Increased
Urine protein	< 4 G/24H		> 12 G/24H
Bone lesions	0 or 1		Many

Durie-Salmon staging system

TREATMENT OF PLASMA CELL DYSCRASIAS



CHEMOTHERAPY FOR MYELOMA

Transplant-eligible	Transplant-ineligible
CyBorD 4 to 8 cycles Stem cell collection High dose melphalan and autologous stem cell transplant (1 or 2) Lenalidomide maintenance	Lenalidomide and dexamethasone

CASE 2 CONTINUED

- Patient is admitted to hospital with acute renal failure from hypercalcemia and probable myeloma kidney
- Quantitative immunoglobulins showed IgG 50 G/L, serum free kappa light chain level 20,000 and free kappa/lambda light chain ratio 500
- He is started on aggressive hydration, given zometa 4 mg IV, bone marrow biopsy is performed and he is started on dexamethasone 40 mg daily for 4 days
- Nephrology is consulted but his renal function improves
- When results of bone marrow biopsy and SPEP are available, he is started on chemotherapy

CASE 3

- 45 year old male presents with 1 week of fatigue, easy bruising, a rash on his legs and epistaxis
- He has no B symptoms
- He has petechiae on examination, and lots of bruises
- WBC 2.1, hemoglobin 72, platelets 9, LD 1245, INR 2.3, PTT 62, fibrinogen 1.3, D-dimer high

- The Hematopathologist tells you he sees promyelocytes on the peripheral blood smear

ACUTE LEUKEMIA

- Incidence 4/100,000

- Normal hematopoiesis is suppressed:
  - anemia (fatigue)
  - thrombocytopenia (bleeding)
  - neutropenia (infections)
- DIC (especially with acute promyelocytic leukemia or APL)
- Lymphadenopathy and CNS symptoms with ALL
- Gum hypertrophy, skin infiltration rarely

Age-standardized incidence rate from Canadian Cancer Statistics 2017

DIAGNOSIS

- Bone marrow aspirate and biopsy
  - Morphology
  - Special stains
  - Flow cytometry
  - Cytogenetics
  - Molecular

ACUTE PROMYELOCYTIC LEUKEMIA

- AML associated with t(15;17) or APL-RARα fusion gene
- Cure rate > 80% if survive the first week of treatment

- Death rate from DIC bleeding complications high (10 to20%)
  - START TREATMENT WITH ATRA ASAP
  - Treat DIC with blood and platelet transfusions, cryoprecipitate or FFP

CHEMOTHERAPY

- Induction chemotherapy to achieve complete remission
- Consolidation chemotherapy to maintain complete remission or cure
  - High-dose cytarabine x 3 cycles
  - Allogeneic stem cell transplant for poor risk cytogenetics, induction failures, second remissions, secondary or therapy-related leukemias
- +/- Maintenance therapy
- +/- CNS prophylaxis

TUMOR LYSIS SYNDROME

- Occurs when there is rapid and massive cell kill with chemotherapy
  - Usually for leukemia/lymphoma with bulky disease
- Causes high uric acid (urate), renal failure, hyperkalemia

- Prevent and treat with hydration, alkalinization of urine, and Allopurinol or Rasburicase

SUPPORTIVE THERAPY

- Transfusion when:
  - Hb < 80
  - Platelets < 10
    - If febrile, transfuse if < 20
    - If bleeding, transfuse until > 30-50
    - If on anticoagulation, keep plt > 30
- Prophylactic antibiotics with Septra, Pentamidine, Acyclovir, Fluconazole

FEBRILE NEUTROPENIA

- If temp > 38.3 or > 38.0 for more than 1 hr and ANC < 0.5
  - Call MD
  - Blood and urine cultures, CXR
  - Start broad- spectrum antibiotics within 1-2 hrs
- Avoid using Tylenol or anti-inflammatory meds since this will mask fever (often the only sign of infection)

CASE 3 CONTINUED

- The Hematologist on call is contacted immediately
- Arrangements are made to transfer the patient to the QEII as soon as possible after a platelet transfusion
- The Hematologist on call is waiting in the QEII ER
- Repeat bloodwork is done, and flow cytometry and molecular testing is performed immediately
- The patient is given cryoprecipitate and a blood transfusion
- ATRA is administered within 4 hours of the initial call
- Bone marrow biopsy is performed the next morning

CASE 4

- 74 year old male has an incidental finding of WBC 30 on routine annual bloodwork
- He has no B symptoms
- His examination is normal
- WBC 30, hemoglobin 144, platelets 167
  - The peripheral blood smear shows increased numbers of lymphocytes and smear cells

- You order flow cytometry on the peripheral blood

CLL

- Incidence 10/100,000

- Presentation
  - Lymphadenopathy and splenomegaly
  - Anemia and thrombocytopenia from marrow infiltration
  - Immune dysregulation (autoimmune hemolytic anemia, ITP, recurrent infections, aggressive skin cancer)

- Richter's transformation to DLBCL

Age-standardized incidence rate from Canadian Cancer Statistics 2017

DIAGNOSIS

- Peripheral blood shows increased small lymphocytes and smear cells
- Flow cytometry on blood, marrow or lymph node
  - CD19+, CD20+ (B-cell markers)
  - CD5+ (T-cell marker)
- AIHA (anemia, high reticulocyte count, high LD, high bilirubin, low haptoglobin, DAT positive, spherocytes)
- ITP (thrombocytopenia with no other explanation)

STAGING

Stage		Survival (months)
A	Fewer than 3 involved lymphoid sites	Normal
B	3 or more involved lymphoid sites	84 months
C	Presence of Hb < 100 and/or platelet < 100	24 months

Binet staging system

CLL is treatable with chemotherapy, but not curable

CHEMOTHERAPY

Young and fit	Elderly and fit	Elderly and frail
Watch and wait		
Fludarabine, cyclophosphamide and rituximab (FCR) x 6 cycles Ibrutinib if poor risk	Bendamustine and rituximab x 6 cycles	Obinotuzumab and chlorambucil Ibrutinib

CASE 4 CONTINUED

- Patient is diagnosed with stage A CLL
- He is on a watch-and-wait protocol since he is asymptomatic

- Patient presents with increasing fatigue a year later and weakness
- WBC 40, hemoglobin 60, platelet count 166
- Reticulocyte count is high, LD 850, bili 46, DAT 4+ positive, haptoglobin < 0.05
- Patient is started on prednisone 1 mg/kg/day, and transfused blood the next day (RBC antigen matched blood)

CML

- Incidence 1/100,000

- Presentation
  - Usually incidental finding
  - Anemia and thrombocytopenia from marrow infiltration
  - Splenomegaly

- Progresses to blast crisis (AML or ALL)
- Stable chronic phase can have near-normal survival

Age-standardized incidence rate from Canadian Cancer Statistics 2017

DIAGNOSIS

- Associated with t(9;22), Philadelphia chromosome
  - Bone marrow cytogenetics or FISH testing
- BCR-ABL fusion gene
  - Peripheral blood or marrow molecular testing

TREATMENT

Generic tyrosine kinase inhibitor	Brand name	Side effects
Imatinib	Gleevec	Vomiting, diarrhea, rash, arthralgia
Nilotinib	Tasigna	Hyperglycemia, increased LFTs, rash Cardiovascular complications
Dasatinib	Sprycel	Pleural effusions Pulmonary hypertension
Bosutinib	Bosulif	Diarrhea
Ponatinib	Iclusig	Rash, pancreatitis Cardiovascular complications
All cause fatigue, heart arrhythmias and heart failure		

MPD AND MDS

- Both are clonal disorders of hematopoietic stem cells
- Myeloproliferative disorders (MPD)
  - Purposeless proliferation of one or more of the myeloid cell lines
- Myelodysplastic syndromes (MDS)
  - A heterogeneous group of acquired clonal hematopoietic stem cell disorders characterized by ineffective hematopoiesis
  - Progressive cytopenias and progression to AML

Myeloproliferative Disorders	Atypical Myeloproliferative Disorders
Polycthemia vera Essential thrombocythemia Chronic myeloid leukemia Primary myelofibrosis Chronic neutrophilic leukemia Chronic eosinophilic leukemia Mast cell disease	Chronic myelomonocytic leukemia Juvenile myelomonocytic leukemia Atypical chronic myeloid leukemia Unclassifiable MDS/MPD
	Myelodysplastic Syndromes

INDICATIONS FOR BONE MARROW BIOPSY

- Persistent or progressive unexplained cytopenia or cytosis for more than 12 months
  - Especially if more than 1 cell line is affected
- Unexplained macrocytosis
- Normal B12, folate and ferritin levels
- History of chemotherapy or radiation

MDS

- Incidence 4.1/100,000
- Presentation
  - Usually incidental finding
  - Fatigue
  - Symptoms from anemia, thrombocytopenia or neutropenia
- Death from progression to AML or complication from cytopenias (bleeding, sepsis, iron overload)

DIAGNOSIS

- Bone marrow aspirate and biopsy with flow cytometry and cytogenetics
  - Hypercellular marrow
  - Dysplastic morphology in 1 or more cell lines
  - Increase in blast count 5-20%
  - Abnormal cytogenetics
    - -5/del 5q, -7/del 7q, +8, 17p-, del 20q
    - -Y (can be normal in older males)

IPSS

Prognostic variable	0	0.5	1.0	1.5	2.0
BM blasts (%)	<5	5-10	-	11-20	21-30
Karyotype	Good	Int.	Poor		
Cytopenias	0/1	2/3			

IPSS CONT.

Risk	Overall score	Median survival	25% AML progression
LOW	0	5.7 years	9.4 years
INT-1	0.5-1.0	3.5 years	3.3 years
INT-2	1.5-2.0	1.1 years	1.1 years
HIGH	≥2.5	0.4 years	0.2 years

MANAGEMENT OF MDS

- Management decision can be difficult due to heterogeneity of MDS

- 4 major goals
  - Control of symptoms
  - Improve QOL (minimize toxicity of therapy)
  - Improve overall survival
  - Decrease progression to acute leukemia

- Based on age, well-being, IPSS category

TYPES OF THERAPY FOR MDS

High Intensity	Low Intensity	Supportive Care
Age <60 years Selected pts>60 Good health Int-2, High IPSS	Age <60 with Int-1/Low IPSS Age >60 in good health	Poor health
AML chemotx or Vidaza ± allogeneic SCT	EPO ± G-CSF Revlimid Vidaza or Decitabine	Transfusions Antibiotics Iron chelation therapy

MPD

- Incidence for ET, PV, PMF each 1/100,000

- Routine CBC shows increased counts
- Vasomotor symptoms, pruritis, erythromelalgia, and gout
- Splenomegaly
- Main complications is thrombosis, arterial and/or venous, in unusual locations
- Myelofibrosis can develop marrow failure, portal hypertension and heart failure from massive hepatosplenomegaly
- Can evolve to myelofibrosis or AML

Disorder	RBCs	WBCs	Platelets	Marrow Fibrosis	Ph chrom.	Spleen Size
ET	±	±	+++	± (late)	0	±
PV	+++	++	++	+ (late)	0	++
CML	±	+++	++	± (late)	+	++
CIMF	±	±	±	+ to +++	0	+++

DIAGNOSIS

- Peripheral blood molecular testing
  - JAK 2 mutation (95% PV, 50% ET and PMF)
  - CALR and other mutations for ET and PMF
- Bone marrow biopsy looking for fibrosis

TREATMENT

- Aspirin 81 mg daily
- Hydroxyurea or anagrelide
  - In patients at high risk for thrombotic complications

- Primary myelofibrosis has more aggressive course
  - Ruxolitinib for DIPSS intermediate or high risk
  - Allogeneic stem cell transplant for selected patients

SUMMARY

- Learn to recognize signs of hematologic malignancy
  - Abnormal CBC
- Know when to refer to a Hematologist
  - Almost always
- When is an urgent referral appropriate?
  - APL, spinal cord compression, SVC syndrome, acute kidney injury, hypercalcemia, tumour lysis syndrome…
- Learn about some useful diagnostic or staging investigations
  - CBC, flow cytometry, molecular testing, CT scan, bone marrow biopsy