Myelodysplastic Syndromes (MDS)

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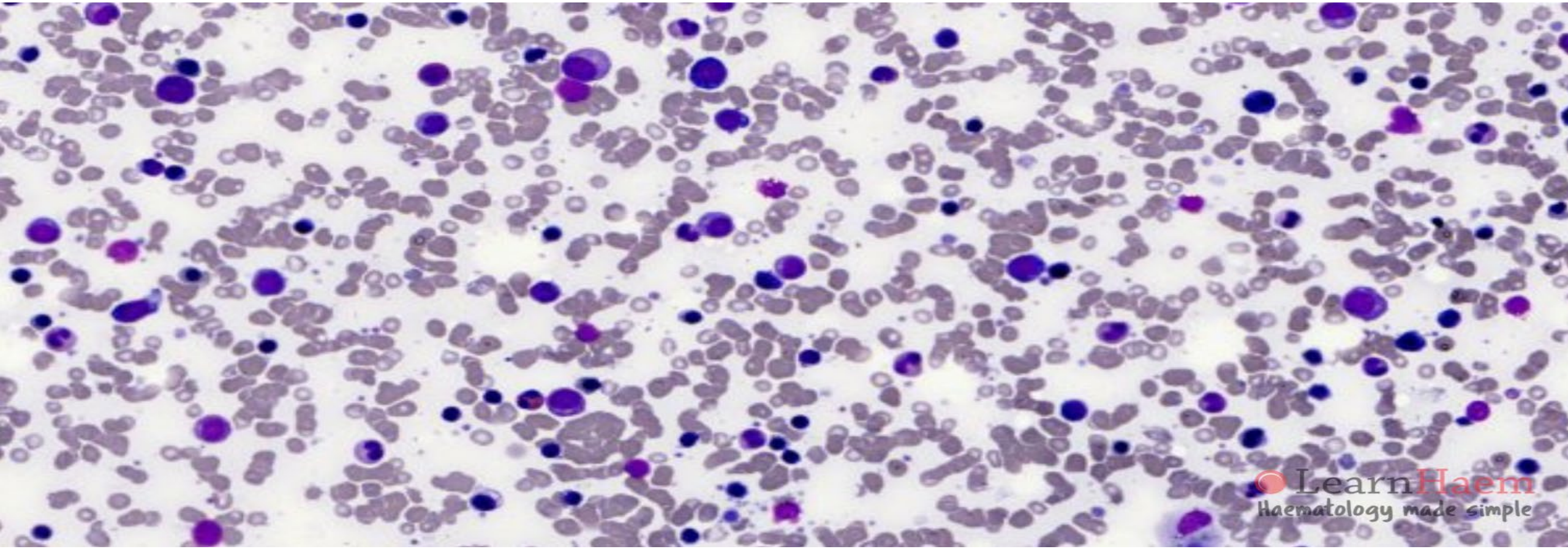
What is myelodysplasia?



https://www.learnhaem.com/courses/frcpath-morph/lessons/myelodysplastic-syndromes-2/topic/mds-overview/

What is myelodysplasia?

–clonal disorder of myeloid stem cells

– may occur de novo or secondary to various insults to the bone marrow.

–environmental and iatrogenic etiologies have been implicated in MDS

–exposure to chemotherapy (alkylating agents in particular),

– radiation

–environmental toxins such as benzene.

– Familial MDS has been reported but is a rare entity.

–researchers can identify one or more driver mutations in up to 80% to 90% of patients with some of the most common ones including *SF3B1, TET2, SRSF2, ASXL1, DNMT3A, RUNX1, U2AF1, TP53*, and *EZH2.*

–e.g. *RUNX1* is a mutation noted to disrupt normal hematopoiesis.

–CBC usually reveals anemia or pancytopenia. There is no one histopathologic feature that defines MDS but rather a constellation of findings from the peripheral blood and bone marrow which meet the accepted criteria for diagnosis.

OBJECTIVES

- CBC 101
- Anemias
- MDS
- Treamtment
- Expectations

CBC 101

CBC With Differential/Platelet				
WBC	3.6	x10E3/uL	3.4-10.8	02
RBC	4.15	x10E6/uL	3.77-5.28	02
Hemoglobin	12.9	g/dL	11.1-15.9	02
Hematocrit	39.3	%	34.0-46.6	02
MCV	95	fL	79-97	02
MCH	31.1	pg	26.6-33.0	02
MCHC	32.8	g/dL	31.5-35.7	02
RDW	13.3	%	12.3-15.4	02
Platelets	256	x10E3/uL	155-379	02
Neutrophils	46	%	40-74	02
Lymphs	41	%	14-46	02
Monocytes	9	%	4-12	02
Eos	3	%	0-5	02
Basos	1	%	0-3	02
Neutrophils (Absolute)	1.7	x10E3/uL	1.4-7.0	02
Lymphs (Absolute)	1.5	x10E3/uL	0.7-3.1	02
Monocytes(Absolute)	0.3	x10E3/uL	0.1-0.9	02
Eos (Absolute)	0.1	x10E3/uL	0.0-0.4	02
Baso (Absolute)	0.0	x10E3/uL	0.0-0.2	02
Immature Granulocytes	0	%	0-2	02
Immature Grans (Abs)	0.0	x10E3/uL	0.0-0.1	02

CBC 101

WBC	8.81	-	[10^3/uL]		
RBC	6.14	+	[10^6/uL]		
HGB	11.9		[g/dL]		
HCT	37.1		[%]		
MCV	60.4	-	[fL]		
MCH	19.4	-	[pg]		
MCHC	32.1		[g/dL]		
PLT	415	+	[10^3/uL]		
RDW-SD			[fL]		
RDW-CV	14.7	+	[%]		
PDW			[fL]		
MPV	10.1		[fL]		
P-LCR			[%]		
PCT			[%]		
NEUT			[10^3/uL]	48.6 *	[%]
LYMPH			[10^3/uL]	35.4 *	[%]
MONO			[10^3/uL]	10.0 *	[%]
EO			[10^3/uL]	5.3 *	[%]
BASO			[10^3/uL]	0.7	[%]
NRBC			[10^3/uL]		[/100WBC]
RET			[%]		[10^6/uL]
IRF			[%]		
LFR			[%]		
MFR			[%]		
HFR			[%]		

Healthy 42 year old southeastern asian female establishing care- PCP is seeing for the first time. Normal menses. G3P and took prenatals. She notes that she has been told she w anemic in the past. No h/o PRBCs. Feels well overall witho change, active. Ferritin level pending.

a. Normal CBC
b. Iron deficiency anemia
c. Vitamin B12 deficiency
d. Thalassemia
e. Myelodysplasia

CBC 101

WBC	8.81	-	[10^3/uL]		
RBC	6.14	+	[10^6/uL]		
HGB	11.9		[g/dL]		
HCT	37.1		[%]		
MCV	60.4	-	[fL]		
MCH	19.4	-	[pg]		
MCHC	32.1		[g/dL]		
PLT	415	+	[10^3/uL]		
RDW-SD			[fL]		
RDW-CV	14.7	+	[%]		
PDW			[fL]		
MPV	10.1		[fL]		
P-LCR			[%]		
PCT			[%]		
NEUT			[10^3/uL]	48.6 *	[%]
LYMPH			[10^3/uL]	35.4 *	[%]
MONO			[10^3/uL]	10.0 *	[%]
EO			[10^3/uL]	5.3 *	[%]
BASO			[10^3/uL]	0.7	[%]
NRBC			[10^3/uL]		[/100WBC]
RET			[%]		[10^6/uL]
IRF			[%]		
LFR			[%]		
MFR			[%]		
HFR			[%]		

Healthy 45 year old southeastern asian female establishing
care- PCP is seeing for the first time. Normal menses. G3P
Feels well overall without change, active.

a. Normal CBC
b. Iron deficiency anemia
c. Vitamin B12 deficiency
d. Thalassemia
e. Myelodysplasia

- 10/06/23 10:55
- White Blood Count: 3.03 (L)
- Hemoglobin: 6.1 (L)
- Hematocrit: 18.3 (L)
- Platelet Count: 41 (L)
- Neutrophil: 34.6
- Lymphocyte: 58.7 (H)
- Monocyte: 1.0
- Eosinophil: 0.0
- Basophil: 0.0
- Abs Neutrophils: 1.05 (L)
- Abs Lymphocytes: 1.78
- Abs Monocytes: 0.03 (L)
- Abs Eosinophils: 0.00 (L)
- Abs Basophils: 0.00 (L)
- Metamyelocyte: 1.9 (H)
- Myelocyte: 1.9 (H)
- Blast: 1.9 (H)
- Red Blood Cell Count: 1.58 (L)
- MCV: 115.8 (H)
- MCH: 38.6 (H)
- MCHC: 33.3

85 yo female presenting with fatigue to PCP.

a. Normal CBC
b. Iron deficiency anemia
c. Vitamin B12 deficiency
d. Thalassemia
e. Myelodysplasia

- 10/06/23 10:55
- White Blood Count: 3.03 (L)
- Hemoglobin: 6.1 (L)
- Hematocrit: 18.3 (L)
- Platelet Count: 41 (L)
- Neutrophil: 34.6
- Lymphocyte: 58.7 (H)
- Monocyte: 1.0
- Eosinophil: 0.0
- Basophil: 0.0
- Abs Neutrophils: 1.05 (L)
- Abs Lymphocytes: 1.78
- Abs Monocytes: 0.03 (L)
- Abs Eosinophils: 0.00 (L)
- Abs Basophils: 0.00 (L)
- Metamyelocyte: 1.9 (H)
- Myelocyte: 1.9 (H)
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85 yo female presenting with fatigue to PCP.

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CBC 101

- Anemia as measured by HGB
  - <13 g/dL in men
  - <12 g/dL in women
- Reticulocyte index = reticulocyte % x hgb / normal hemoglobin
  - </= 2% is hypoproliferative
- Is the anemia microcytic (MCV <80fl), normocytic (MCV 80-100fl) or macrocytic (MCV >100fl)
- **Classically MDS is a macrocytic hypoproliferative anemia presentation**
  - leukopenia
  - thrombocytopenia

Macrocytic hypoproliferative anemia differential

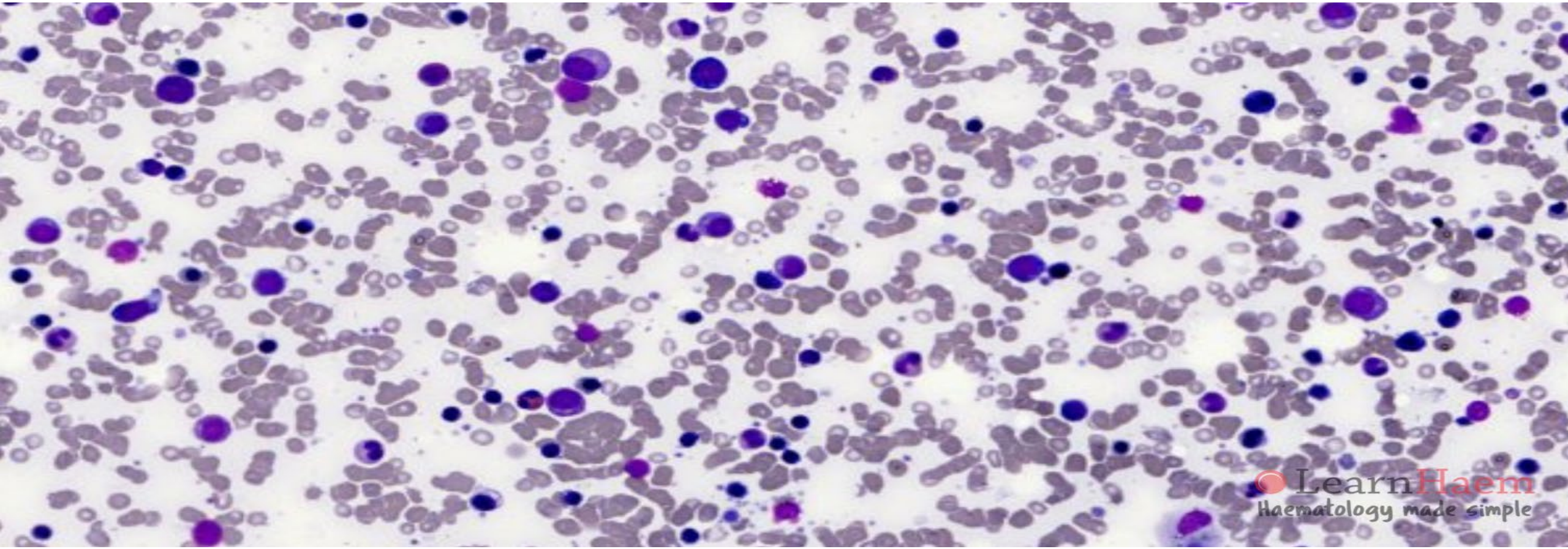
- Vitamin B-12 deficiency
  - diminished intake (malnutrition)
  - malabsorptive states (atrophic gastritis either autoimmune or non-autoimmune from *Helicobacter pylori* or Zollinger-Ellison syndrome, Diphyllobothrium tapeworm infection, gastric bypass, ileal resection)
- Folate deficiency
  - diminished intake (alcohol abuse or malnutrition)
  - increased consumption (hemolysis or pregnancy)
  - malabsorption (familial, gastric bypass, or medications like cholestyramine or metformin)
- Liver disease
- Alcoholism
- Hypothyroidism
- certain medications
  - folic acid analogs (ex. methotrexate, trimethoprim-sulfamethoxazole)
  - nucleic acid analogs (5-fluorouracil, zidovudine)
  - others (hydroxyurea, pentamidine, phenytoin, pyrimethamine, sulfasalazine, triamterene)
- myelodysplastic syndrome

What is your work up????

- Labs- B12 and folate, consider copper or leave to the hem/oncs
- recent thyroid testing? symptoms of hypothyroid?
- Medication review
- History - EtOH, radiation, prior chemo, etc
- peripheral blood smear

- Concern for MDS or other and no clear deficiency- time for heme/onc involvement.

What is myelodysplasia?



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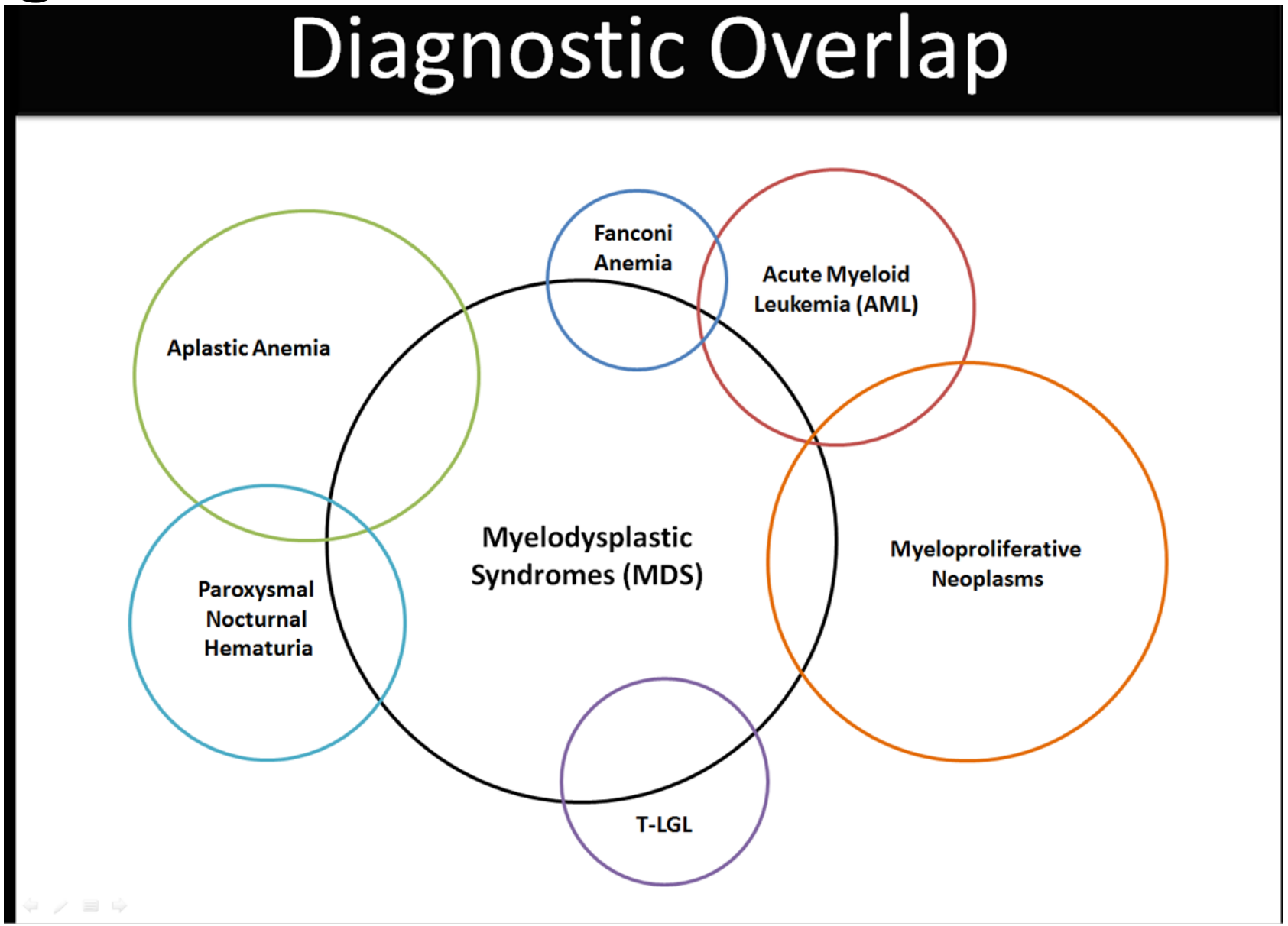
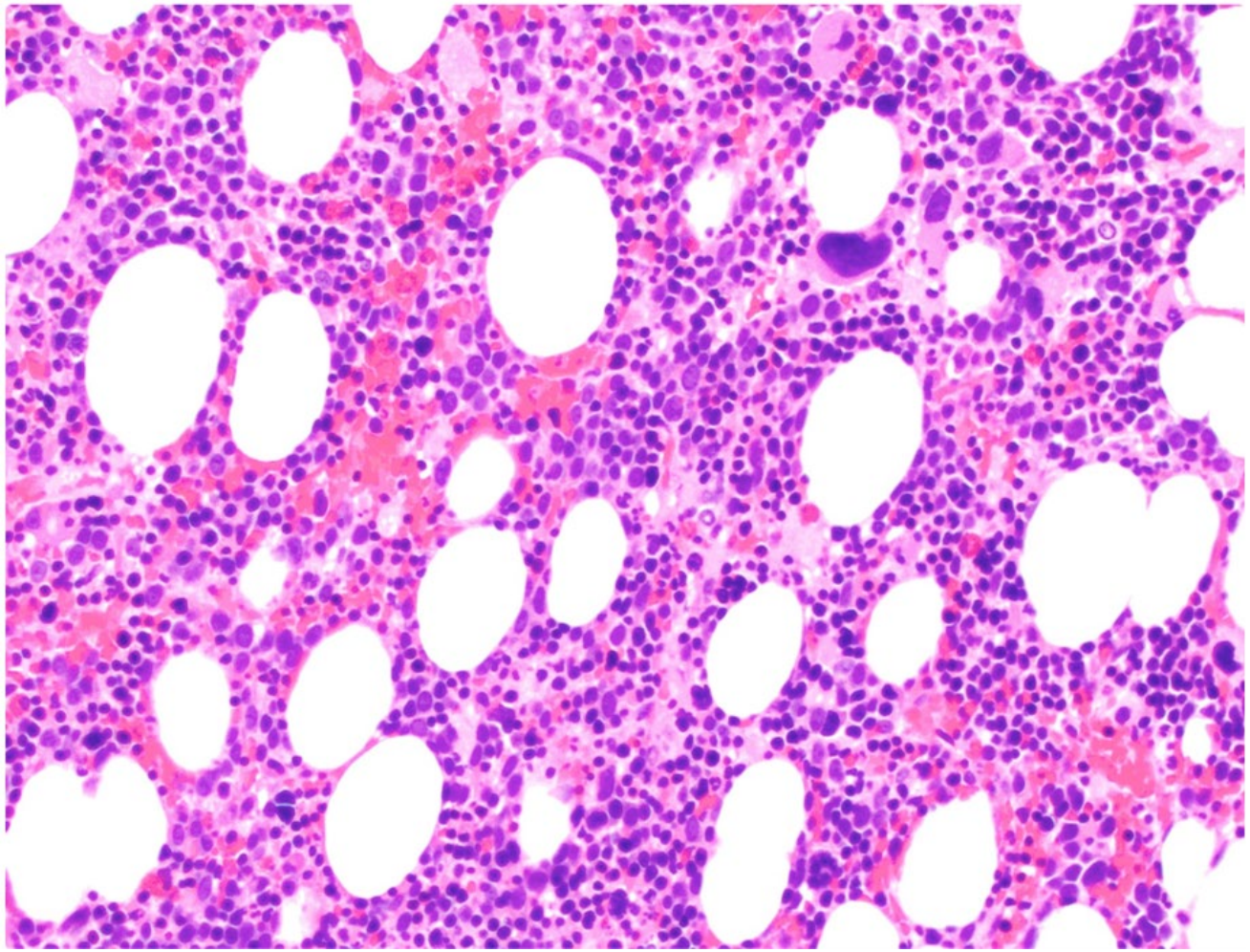
MDS


Diagnostic Overlap
Fanconi Anemia
Acute Myeloid Leukemia (AML)
Aplastic Anemia
Myelodysplastic Syndromes (MDS)
Myeloproliferative Neoplasms
Paroxysmal Nocturnal Hematuria
T-LGL

MDS

- Incidence 3–4 individuals per 100000 in the US population
- Prevalence increases with age
- In individuals age 60 and above, prevalence is 7–35 per 100000
- Median age at diagnosis of MDS is ~70 years and <10% are younger than 50 years
- more frequently males than females
- no known ethnic differences in the incidence of MDS,
  - But….Asian populations, MDS tends to occur at an earlier age, more often with a hypocellular marrow and less often with isolated 5q deletion (‘5q-syndrome’).
  - Trisomy 8 also seems to occur more frequently in Asian populations compared with Western populations
- etiology of MDS is only known in 15% of cases
  - Exposure to prior chemo or radiation therapy is a risk for the development of MDS
    - military

Diagnosis- Bone Marrow Biopsy and Aspirate



- General
  - majority of cases are normocellular or hypercellular
  - Erythroid hyperplasia
  - Myeloid hyperplasia with left shift
- Erythroid lineage dysplasia
  - multinuclearity, megaloblastoid changes
  - ring sideroblasts (< 15%
- Myeloid lineage dysplasia
  - Small or unusually large size
  - Nuclear cytoplasmic asynchrony
  - Nuclear hyposegmentation (pseudo Pelger-Huët anomaly)
  - Nuclear hypersegmentation
  - Decreased granules; agranularity
- Megakaryocyte dysplasia
  - Micromegakaryocytes (most reliable and reproducible)
  - Nuclear hypolobation or nonlobation
  - Binucleation or multinucleation

Photo Contributed by Julia T Geyer, MD; https://www.pathologyoutlines.com/topic/myeloproliferativeRCMD.html

The classification of MDS by WHO (2022) is as follows - replacing 2016 Guidlines:

MDS genetically defined

- MDS-5q (low blasts) — Blasts <5%BM and <2%PB
- MDS-SF3B1 (low blasts) — Blasts <5% BM
- MDS-biTP53 — Blasts <20% BM, PB

MDS, morphologically defined

- MDS with low blasts (MDS-LB) — Blasts <5% BM, 2-4% PB
- MDS, hypoplastic (MDS-h) — Blasts <5% BM
- MDS with increased blasts (MDS-IB)
  a. MDS-IB1 — Blasts 5% to 9% BM or
     2-4% peripheral blood
  b. MDS-IB2 — Blasts 10-19% BM or
     5-19% PB, Auer rods
- MDS with Fibrosis (MDS-f) — Blasts 5-19% BM, 2-19% PB
- AML — Blasts >/=
  20% BM

MDS Scoring systems and Prognosis

Prognostic variable	Score						
	0	0.5	1.0	1.5	2.0	3.0	4.0
Cytogenetics*	Very good		Good		Intermediate	Poor	Very poor
Bone marrow blast (%)	≤2		>2 to <5		5 to 10	>10	
Hemoglobin (g/dL)	≥10		8 to <10	<8			
Platelets (cells/microL)	≥100	50 to 100	<50				
Absolute neutrophil count (cells/microL)	≥0.8	<0.8					

*Cytogenetic definitions:

- Very good: –Y, del(11q)
- Good: Normal, del(5q), del(12p), del(20q), double including del(5q)
- Intermediate: del(7q), +8, +19, i(17q), any other single, double not including del(5q) or –7/del(7q), or independent clones
- Poor: –7, inv(3)/t(3q)/del(3q), double including –7/del(7q), complex: 3 abnormalities
- Very poor: Complex: >3 abnormalities

Risk group	IPSS-R score	Median overall survival (years)	Median time to 25% AML evolution (years)
Very low	≤1.5	8.8	>14.5
Low	>1.5 to 3.0	5.3	10.8
Intermediate	>3 to 4.5	3.0	3.2
High	>4.5 to 6	1.6	1.4
Very high	>6	0.8	0.7

Greenberg PL, Tuechler H, Schanz J, et al. Revised International Prognostic Scoring System for (IPSS-R) myelodysplastic syndromes. Blood 2012.

MDS Treatment

- Symptom management
  - anemia
  - thrombocytopenia
  - neutropenia
- Patients do not always require treatment as long as they are asymptomatic
- MDS often portends an indolent or gradual course - (R-IPSS scoring help determine this) ,
- The only curative modality remains an allogeneic stem cell transplant, but this is often difficult as MDS occurs more commonly in the elderly population.

MANAGEMENT OF LOWER -RISK DISEASE (IPSS-R VERY-LOW -, LOW -, INTERMEDIATE -RISK DISEASE)

lenalidomide - MDS-5q (low blasts) del(5q) ± one other cytogenetic abnormality

Erythropoiesis-stimulating agent (ESA) for EPO <500

hypomethylating agents for EPO >500

luspatercept - MDS-SF3B1 (low blasts) No del(5q) other cytogenetic abnormalities
with ring sideroblasts ⩾15% (or ring sideroblasts ⩾5% with an SF3B1 mutation)

Equine ATG ± cyclosporin A ± eltrombopag (immunosuppressive therapy). Patients generally ≤60 y and with ≤5% marrow blasts, or those with hypocellular marrows, PNH clone positivity, or STAT-3 mutant cytotoxic T-cell clones.

Ivosidenib - mutant IDH1 (mIDH1)

MANAGEMENT OF HIGHER -RISK DISEASE (IPSS-R INTERMEDIATE -, HIGH -, VERY-HIGH -RISK DISEASE)

Is patient a transplant candidate….

Allo-HCT

vs Azacitidine, Decitabine, Oral decitabine and cedazuridine or High intensity chemotherapy (if no response, consider single agent ivosidenib if mIDH1) followed by allo-HCT

vs Clinical trial followed by allo-HCT

What are these drugs?

Lenalidomide

– second generation with immunomodulatory, antiangiogenic, and antineoplastic properties. Cellular activities of lenalidomide are mediated through its target cereblon, a component of a cullin ring E3 ubiquitin ligase enzyme complex.

– inhibits proliferation and induces apoptosis of certain hematopoietic tumor cells

– Immunomodulatory properties – increased number and activation of T cells and natural killer (NK) cells leading to direct and enhanced antibody dependent cell mediated cytotoxicity (ADCC)

Side effects are innumerable and common. But severe grade ¾ not as common and more related to cytopenias, rash and diarrhea.

Phew……

Table 9: Summary of Adverse Reactions Reported in ≥5% of the REVLIMID Treated Patients in del 5q MDS Clinic
Body System Adverse Reactiona 10 mg Overall (N=148) Patients with at least one adverse reaction 148 (100) Blood and Lymphatic System Disorders Thrombocytopenia 91 (61) Neutropenia 87 (59) Anemia 17 (11) Leukopenia 12 (8) Febrile Neutropenia 8 (5) Skin and Subcutaneous Tissue Disorders Pruritus 62 (42) Rash 53 (36) Dry Skin 21 (14) Contusion 12 (8) Night Sweats 12 (8) Sweating Increased 10 (7) Ecchymosis 8 (5) Erythema 8 (5) Gastrointestinal Disorders Diarrhea 72 (49) Constipation 35 (24) Nausea 35 (24) Abdominal Pain 18 (12) Vomiting 15 (10) Abdominal Pain Upper 12 (8) Dry Mouth 10 (7) Loose Stools 9 (6) Respiratory, Thoracic and Mediastinal Disorders Nasopharyngitis 34 (23) Cough 29 (20) Dyspnea 25 (17) Pharyngitis 23 (16) Epistaxis 22 (15) Dyspnea Exertional 10 (7) Rhinitis 10 (7) Bronchitis 9 (6) General Disorders and Administration Site Conditions Fatigue 46 (31) Pyrexia 31 (21) Edema Peripheral 30 (20) Asthenia 22 (15) Edema 15 (10) Pain 10 (7) Rigors 9 (6) Chest Pain 8 (5) Musculoskeletal and Connective Tissue Disorders Arthralgia 32 (22) Back Pain 31 (21) Muscle Cramp 27 (18) Pain in Limb 16 (11) Myalgia 13 (9) Peripheral Swelling 12 (8) (Continued) Table 9: Summary of Adverse Reactions Reported in ≥5% of the REVLIMID Treated Patients in del 5q MDS Clinical Study Body System Adverse Reactiona 10 mg Overall (N=148) Patients with at least one adverse reaction 148 (100) Nervous System Disorders Dizziness 29 (20) Headache 29 (20) Hypoesthesia 10 (7) Dysgeusia 9 (6) Peripheral Neuropathy 8 (5) Infections and Infestations Upper Respiratory Tract Infection 22 (15) Pneumonia 17 (11) Urinary Tract Infection 16 (11) Sinusitis 12 (8) Cellulitis 8 (5) Metabolism and Nutrition Disorders Hypokalemia 16 (11) Anorexia 15 (10) Hypomagnesemia 9 (6) Investigations Alanine Aminotransferase Increased 12 (8) Psychiatric Disorders Insomnia 15 (10) Depression 8 (5) Renal and Urinary Disorders Dysuria 10 (7) Vascular Disorders Hypertension 9 (6) Endocrine Disorders Acquired Hypothyroidism 10 (7) Cardiac Disorders Palpitations 8 (5)

decitabine, azacitidine and decitabine and cedazuridine (Inqovi) **- hypomethylating agents**

Decitabine and azacitidine are nucleoside metabolic inhibitors that exert its effects after phosphorylation and direct incorporation into DNA and inhibition of DNA methyltransferase, causing hypomethylation of DNA and cellular differentiation and/or apoptosis.

Decitabine/azacitidine-induced hypomethylation in cancer cells may restore normal function to genes that are critical for the control of cellular differentiation and proliferation.

Cytidine deaminase (CDA) is an enzyme that catalyzes the degradation of cytidine, including the cytidine analog decitabine. High levels of CDA in the gastrointestinal tract and liver degrade decitabine and limit its oral bioavailability. Cedazuridine is a CDA inhibitor. Administration of cedazuridine with decitabine increases systemic exposure of decitabine.

Side effects

Most common adverse reactions (incidence ⩾ 20%) are fatigue, constipation, hemorrhage, myal mucositis, arthralgia, nausea, dyspnea, diarrhea, rash, dizziness, febrile neutropenia, edema, headache, cough, decreased appetite, upper respiratory tract infection, pneumonia, and transaminase increased. The most common Grade 3 or 4 laboratory abnormalities (≥ 50%) were leukocytes decreased, platelet count decreased, neutrophil count decreased, and hemoglobin decreased.

Ivosidenib- mutant IDH1 (mIDH1)

isocitrate dehydrogenase-1 (IDH1) inhibitor indicated for patients with a susceptible IDH1 mutation

The IDH1 enzyme converts isocitrate to ketoglutarate, leading to the production of NADPH, which plays an important role in energy production and protecting cells from reactive oxygen species.

Ivosidenib SE in relapsed/refractory MDS

The most common adverse reactions including laboratory abnormalities (≥ 25%)

creatinine increased,hemoglobin decrease, arthralgia, albumin decreased, aspartate aminotransferase increased, fatigue, diarrhea, cough, sodium decreased, mucositis, decreased appetite, myalgia, phosphate decreased, pruritus, and rash

luspatercept

a recombinant fusion protein that binds several endogenous TGF-β superfamily ligands, thereby diminishing Smad2/3 signaling.

– decreased abnormally elevated Smad2/3 signaling and improved hematology parameters associated with ineffective erythropoiesis in mice.

–promoted erythroid maturation through differentiation and increasing the percentage of late-stage erythroid precursors (normoblasts) in the bone marrow of mice and increased erythroid precursors in humans, thereby increasing erythropoiesis.

luspatercept SE

The most common (>10%) adverse reactions were fatigue, headache, musculoskeletal pain, arthralgia, dizziness/vertigo, nausea, diarrhea, cough, abdominal pain, dyspnea, COVID-19, edema peripheral, hypertension, and hypersensitivity

–thromboembolism and Extramedullary Hematopoietic (EMH) Masses seen in thalassemia treatment-naïve MDS

How effective are these drugs

phase III trial was conducted (CALGB 9221) which randomized 191 patients to subcutaneous azacitidine at 75 mg/m2/day for 7 days every 28 days *versus* supportive care only [Silverman *et al*. 2002].

– crossover to the azacitidine arm which occurred in nearly half of the patients allowed

- IPSS had not yet been developed

- Responses occurred in 60% of patients in the azacitidine arm (7% CR, 16% PR, 37% HI) compared with 5% receiving supportive care ($p < 0.001$).

- most of the responses were seen in the third and fourth month of treatment

-Median time to leukemic transformation or death was 21 months for azacitidine *versus* 13 months for supportive care ($p = 0.007$).

-Enhancement in quality of life was also found to be significant in patients initially randomized to azacitidine with an improvement in fatigue, dyspnea, physical functioning and psychological distress compared with those in the supportive care arm [Kornblith *et al*. 2002]

Future

immune checkpoint inhibitors, such as sabatolimab, an anti-TIM3 agent

magrolimab, an anti-CD47

venetoclax, BCL-2 inhibitor - restore the process of apoptosis

We are getting better faster than ever before.

A 55-year-old woman presents with progressive fatigue over the past few months. Her past medical history is significant for breast cancer stage IIA diagnosed 5 years ago. Her treatment consisted of mastectomy and locoregional radiation, followed by chemotherapy with adriamycin and cyclophosphamide. On exam, pallor and some bruising on her arms are noted. There is no palpable lymphadenopathy, and the liver and spleen are not palpable. Complete blood count (CBC) shows a white blood cell (WBC) count of 1500/μL, 60% neutrophils, 24% lymphocytes, 12% monocytes, 0% basophils, 2% eosinophils, hemoglobin of 7.5 g/dL, and a platelet count of 80 × 103/μL. The mean corpuscular volume (MCV) is 110 μm3. Other laboratory test results include creatinine 0.8 mg/dL, alanine aminotransferase (ALT) 24 U/L, and aspartate aminotransferase (AST) 20 U/L; levels of B12, folate, and thyrotropin are normal. Erythropoietin level is 36 IU/L.

What cytogenetic abnormality is most likely to be found on analysis of this patient's bone marrow aspirate?

- monosomy 5
- Translocation (t) (8;21), or inversion (inv) (16)
- t(8;14)
- t(9;22)

The patient in question 1 undergoes bone marrow examination and dysplasia is noted in the erythroid and myeloid lineage, with 4% blasts. Karyotyping reveals monosomy 5, 18, 21 and add(22)(p11.2).

What is the best treatment modality for this patient?

Azacitidine or decitabine
Azacitidine or decitabine followed by allogeneic hematopoietic cell transplantation
Erythropoietin and granulocyte-colony stimulating factor
Lenalidomide
Supportive care only

questionss

mahalo