NCCN 10th Annual Congress:
Hematologic Malignancies™

Patient Case Studies & Panel Discussion

Myeloproliferative Disorders, Elderly Myelofibrosis, Hemophagocytic Syndromes

Panelists: Jessica Altman, MD, *Robert H. Lurie Comprehensive Cancer Center of Northwestern University*; Joseph C. Alvarnas, MD, *City of Hope Comprehensive Cancer Center;* Peter L. Greenberg, MD, *Stanford Cancer Institute*

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CASE 1

Peter L. Greenberg, MD
Stanford Cancer Institute

Challenges in Myeloproliferative Neoplasms (MPNs)

- Phenotypic mimicry/less common MPNs: diagnostic issues
- Prognostic risk status: Survival, thrombosis
- Therapy & role of JAK2 mutation inhibitors
- Impact of MPN-associated molecular markers on clinical outcome and phenotypes

Case 1

- A 68yo man presents with headaches & visual disturbances. Past history includes an unprovoked lower extremity DVT treated without recurrence & a bleeding duodenal ulcer 2 years ago which is no longer symptomatic. He lacks pulmonary or constitutional symptoms.
- Physical exam shows mild hypertension, negative fundoscopic exam. Spleen tip palpable 3 cm below the left costal margin. No nodes or edema.

Case 1

CBC:
WBC 16K, Hb 16.5, MCV 79, Hct 49, Platelets 600K

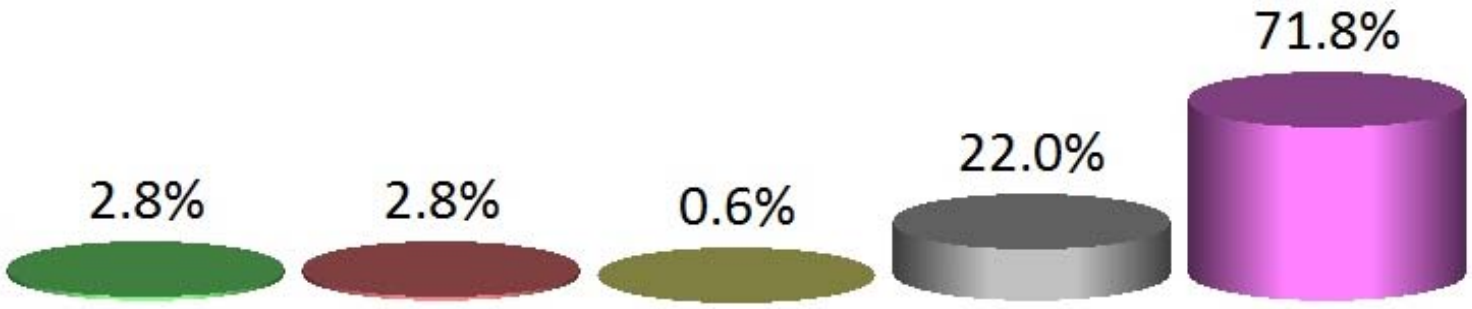
Differential: 60 PMNs, 35 lymphs, 5 monocytes

Peripheral smear:
Mixed micro- and normo-cytic RBCs, 2% retics, large and clumped platelets, normal WBC morphology

ARS Question

1.1: What laboratory studies would you next request?

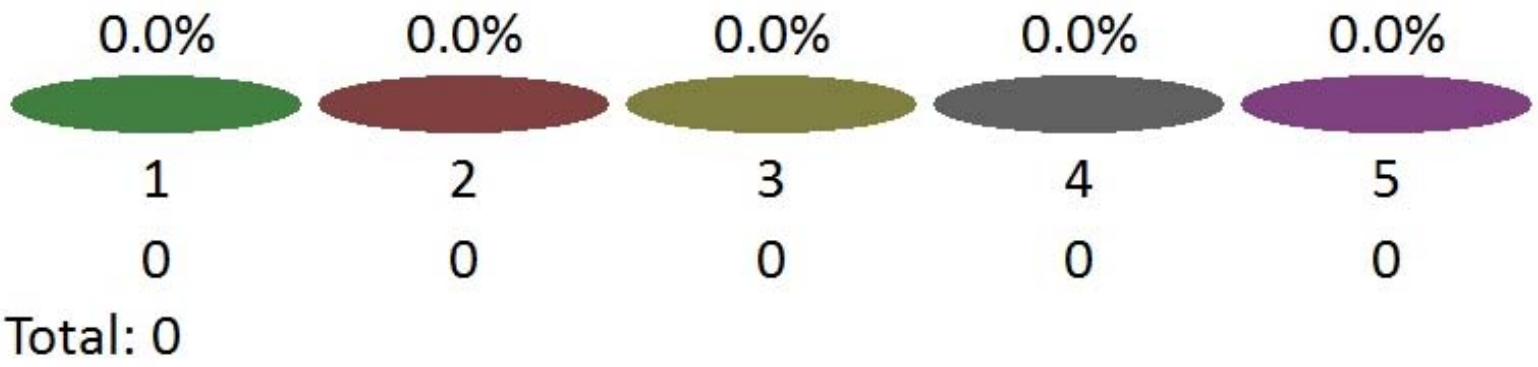
1. Serum creatinine
2. Serum erythropoietin
3. RBC mass (if available)
4. JAK2 mutation analysis
5. 2, 3 and 4



Total: 177

1.2: In your differential, which would be your primary diagnostic consideration?

1. Essential thrombocythemia (ET)
2. Reactive thrombocytosis
3. Polycythemia vera (PV)
4. Secondary polycythemia
5. Myelofibrosis (MF)



Myeloproliferative Neoplasms

- Classical: PV, ET, MF, CML
- Less common: Chronic neutrophilic leukemia (CNL), mastocytosis, CEoL, MPN-U
- MDS/MPNs
  - CMML, JMML
  - Atypical CML, BCR-Abl1 negative
  - MDS/MPN-U (‘Overlap syndrome’)
  - RARS-T (provisional)

WHO, 2008

Diagnostic Criteria for PV

- Major criteria
  - Hb >18.5 Male, >16.5 Female or ↑RBC mass
  - *JAK2*^{V617F} or *JAK2* exon 12 mutation
- Minor criteria
  - Marrow panmyelosis
  - ↓Serum epo
  - Endogenous erythroid colony formation

ET: Distinctions from Other MPNs or Secondary Thrombocytoses

- Platelets >450K, ↑enlarged megakaryocytes, *JAK2*^{617F} mutation or other clonal marker
  - Rule out reactive thrombocytosis, iron deficiency
  - Consider '**masked PV**'
    - **Hct ≥49M, 48F or Hb ≥16.5 M, 16F if *JAK2*m+ & iron deficient**
  - Absence of peripheral blood/marrow features of MF
  - Absence of dyserythropoietic features of RARS-T
  - *BCR-ABL* mutation negative

Distinction between ET and Prefibrotic MF

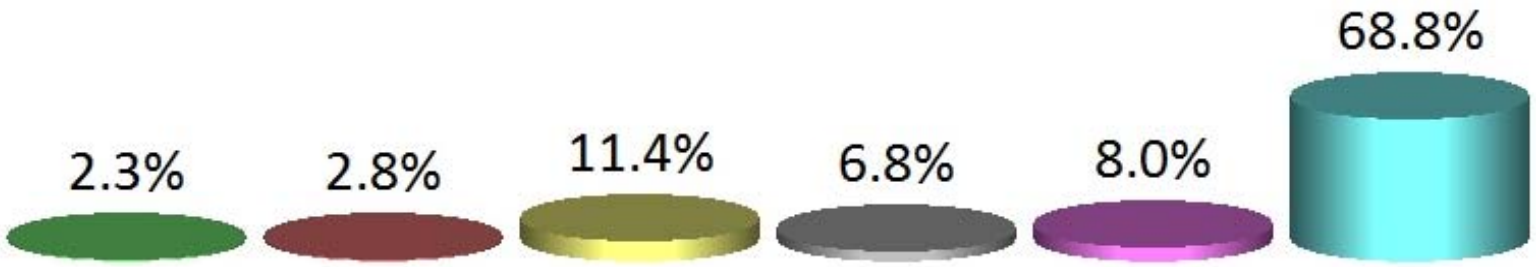
- Prefibrotic MF > ET
  - Anemia, leukocytosis, splenomegaly, megakaryocytic atypia, hypercellularity w/ granulocytic predominance
  - Leukoerythroblastic peripheral smear, tear drop RBCs

Kvasnicka & Thiele, Am J Hematol 85:62, 2010

ARS Question

1.3: What initial therapy would you consider for him?

1. Aspirin
2. Anagrelide
3. Hydroxyurea
4. Ruxolitinib
5. Phlebotomy
6. 1, 3, 5



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Prognostic Risk Systems in MPNs

Clinical Features	DIPSS/MF, N=993	IPSET, N=867	PV, N=1545
Anemia	**XX**		
WBCs	**X**	**X**	**X**
Blasts, PB	**X**		
Constitutional sx	**X**		
Age	**X**	**X**	**X**
Karyotype	**X**		
Platelets <100K/Prior Thrombosis	**X**	**X**	**X**
RBC Transfusion dependence	**X**		
Subgroup Survival	1.3-3-7-15 yrs	14-25-NR yrs	11-19-27 yrs
	Gangat, JCO 2011	Passamonti, Blood 2012	Tefferi, Leuk 2013

Determinants of Thrombotic Risk in PV, ET, MF

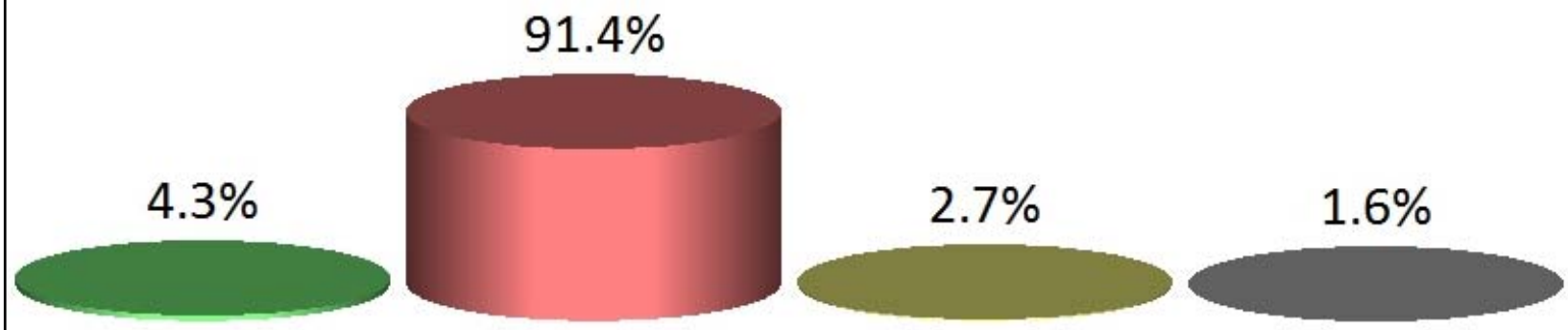
- Age, prior thrombotic history
- Leukocytosis, *JAK2* mutation burden
- Platelet, leukocyte, endothelial activation; protein C resistance; inflammation; c-microparticles

Falanga et al, Sem Thrombosis Hemostasis 40:348, 2014

ARS Questions

1.4: What is the initial aim of your therapy?

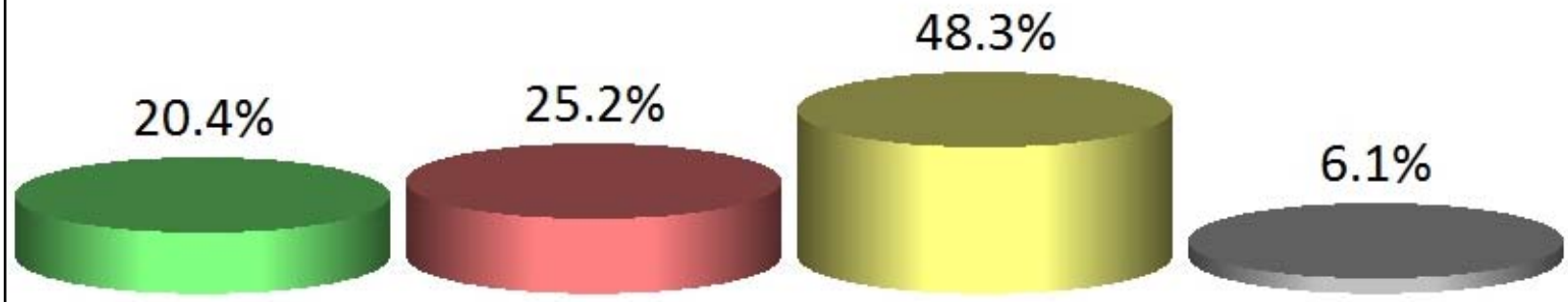
1. Control WBC
2. Decrease hematocrit to <45 & platelet count to <600K
3. Treat iron deficiency
4. Decrease splenomegaly



Total: 185

1.5: Although initial good control of his platelet level and hematocrit occurred, he is now resistant to hydroxyurea. What is your next treatment approach?

1. Phlebotomy
2. Anagrelide
3. Ruxolitinib
4. Peg-Interferon



Ruxolitinib Therapy in Hydroxyurea-Resistant PV patients

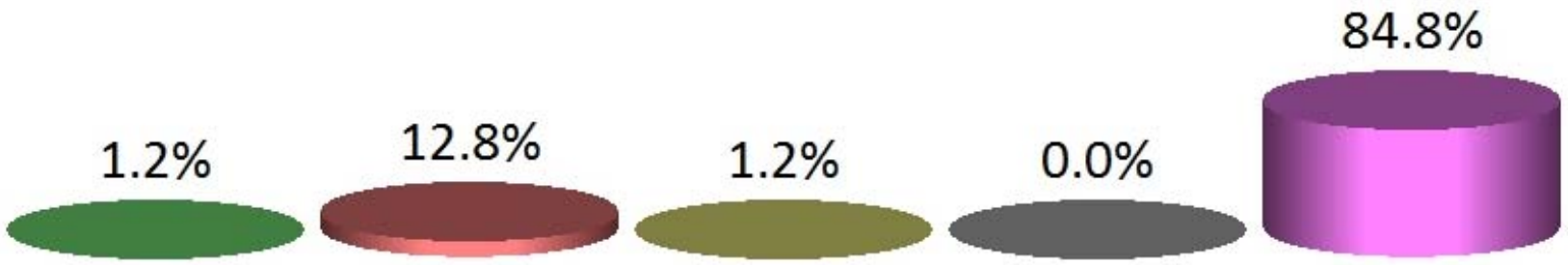
- Complete response 59%
- Phlebotomy independence 60%
- ↓PV-related symptoms
- ↓Thromboses

Vannucchi et al, NEJMed 372:426, 2015

ARS Question

1.6: What molecular features contribute to the diagnosis and prognosis of MPNs?

1. *CALR* mutation
2. *JAK2* mutation
3. *MPL* mutation
4. *BRAF* mutation
5. 1, 2, and 3



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Mutations in MPNs

MPNs	MUTATIONS
Polycythemia Vera	*JAK2^{V617F}, JAK2exon 12, LNK, (TET2)*
Essential Thrombocythemia	*JAK2V^{617F}, CALRexon9, cMPL$^{W515L/K}$, (TET2)*
Primary Myelofibrosis	*JAK2^{V617F}, CALRexon9, cMPL$^{W515L/K}$, (TET2)*
Chronic Myeloid Leukemia	*BCR-ABL*
Atypical CML, Chronic Neutrophilic Leukemia	*CSF3R (GCSFR), SETBP1*
Myeloid Neoplasm w/ Eosinophilia	*PDGFRA, PDGFRB, FGFR1*
Systemic Mastocytosis	*KIT^{816V}*
Refractory Anemia w/ Ring Sideroblasts & Thrombocytosis	*SRFB1, JAK2^{V617F}*

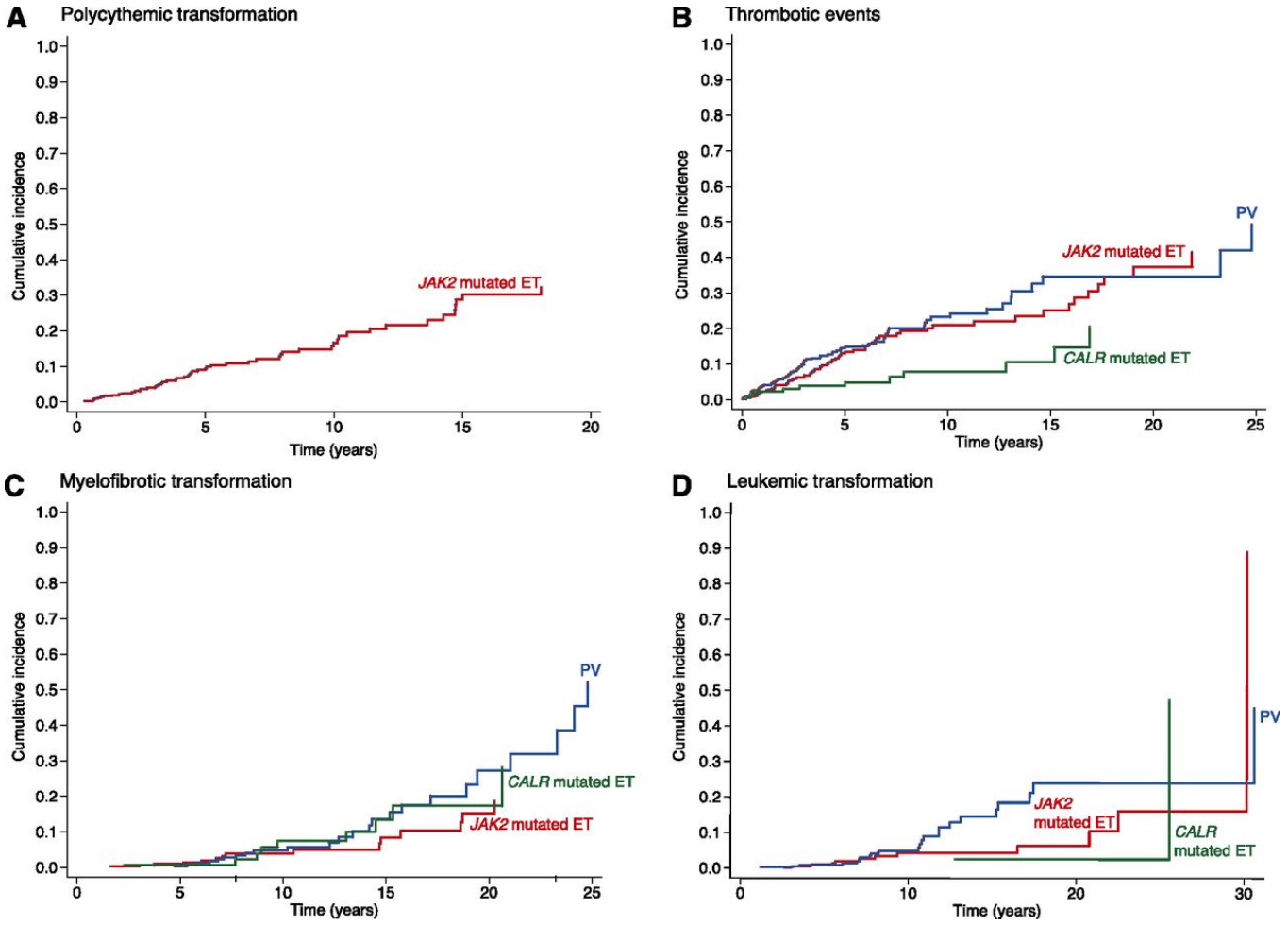
Clinical Outcomes in MPNs

	Survival, years	AML transformation
Polycythemia Vera	14 (11-19-27)	10% @ 20 yr
Essential Thrombocythemia	20 (14-25-NR)	5% @ 20yr
MF	7 (1.3-3-7-15)	5-30%
MF* *CALRm* (23%)	17.7	9.4% @10yr
JAK2m (65%)	9.2	19.4% @10yr
MPLm (4%)	9.1	16.9% @ 10yr
Triple negative (8%)	3.2	34.4%@10yr

PV: Tefferi et al, Leukemia 27: 1874, 2013, n=1545
ET: Passamonti et al, Blood 120:1197, 2012, n=867
MF: Gangat et al, JCO 29: 392, 2011, n=993
MF*: Rumi et al, Blood 124: 1062, 2014, n= 617

Clinical Impact of Mutations in ET Compared to PV

n=1235



Elisa Rumi et al. Blood 2014;123:1544-1551

Effects of Mutation Sequence on MPNs

- *TET2* mutations occur in ~10% of *JAK2m*+ pts by analysis of stem/progenitor clonality:
- *TET2* mutation influenced *JAK2*-related gene proliferative & differentiative expression
- **'*JAK2*m-first' pts** → clinical phenotypes:

  PV/ET > MF, PV > ET, ↑thrombosis, younger,

  (*in vitro*) ruxolitinib responsive

Ortmann et al, NEJMed 372:601, 2015

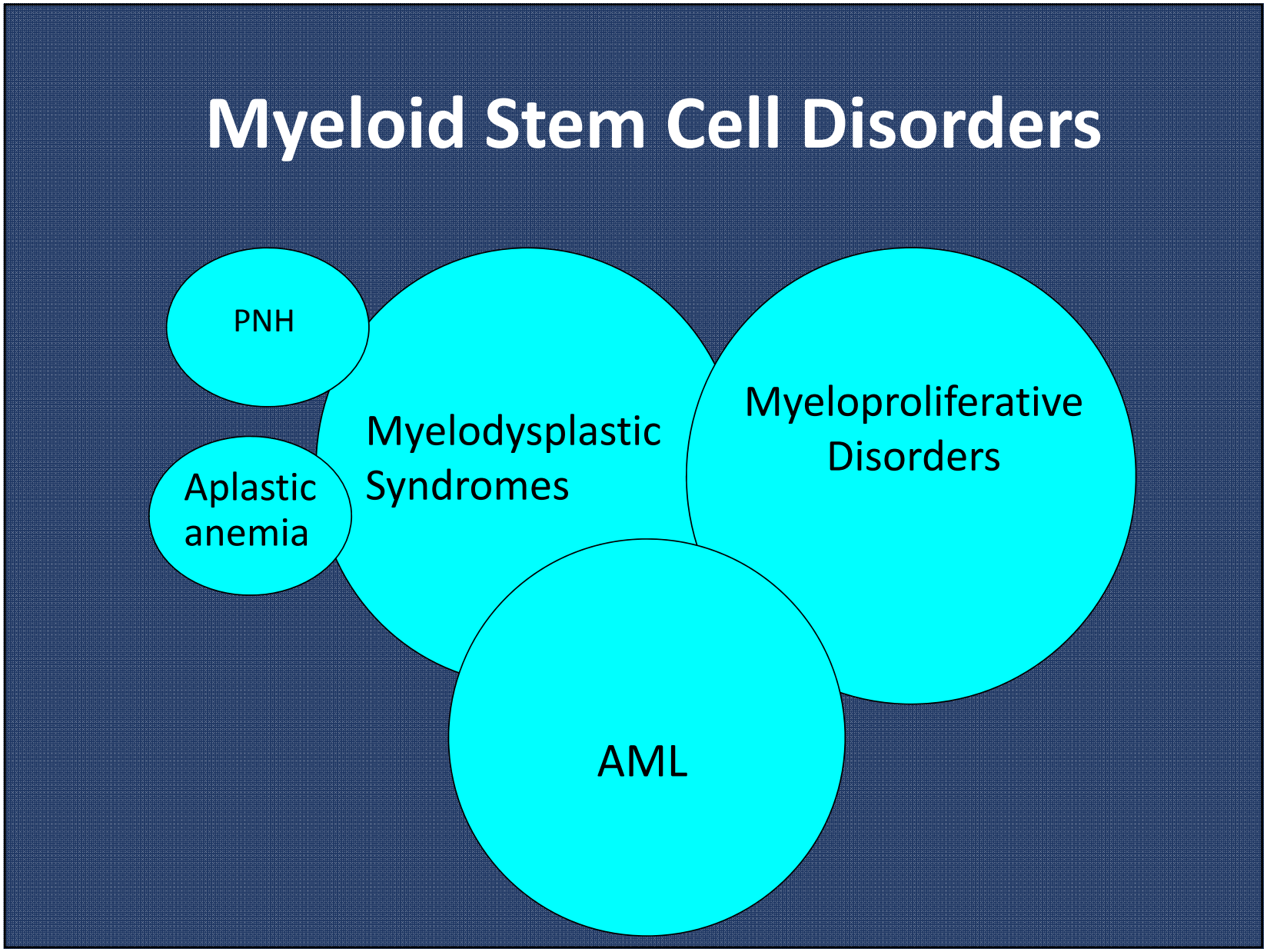
MPNs: Directions

- Comparative trials with therapeutic agents
- New drugs (eg, imetelstat) and combinations (eg, +Interferon) with *JAK2* mutation inhibitors
- Target *CALR* mutations
- Symptom control approaches

CASE 2

Jessica Altman, MD

Robert H. Lurie Comprehensive Cancer Center of Northwestern University



Introduction

- Primary myelofibrosis (PMF) known in the past as agnogenic myeloid metaplasia or chronic idiopathic myelofibrosis
- Most patients with anemia, marked splenomegaly, early satiety, and hypercatabolic symptoms including severe fatigue, low grade fever, night sweats, and weight loss
- Portal hypertension might occur and contribute to variceal bleeding or ascites
- Median survival in the population that comprised International Prognostic Scoring System (IPSS) for PMF was 69 months

  (Cervantes et al. 2009. Blood 113(13):2895)

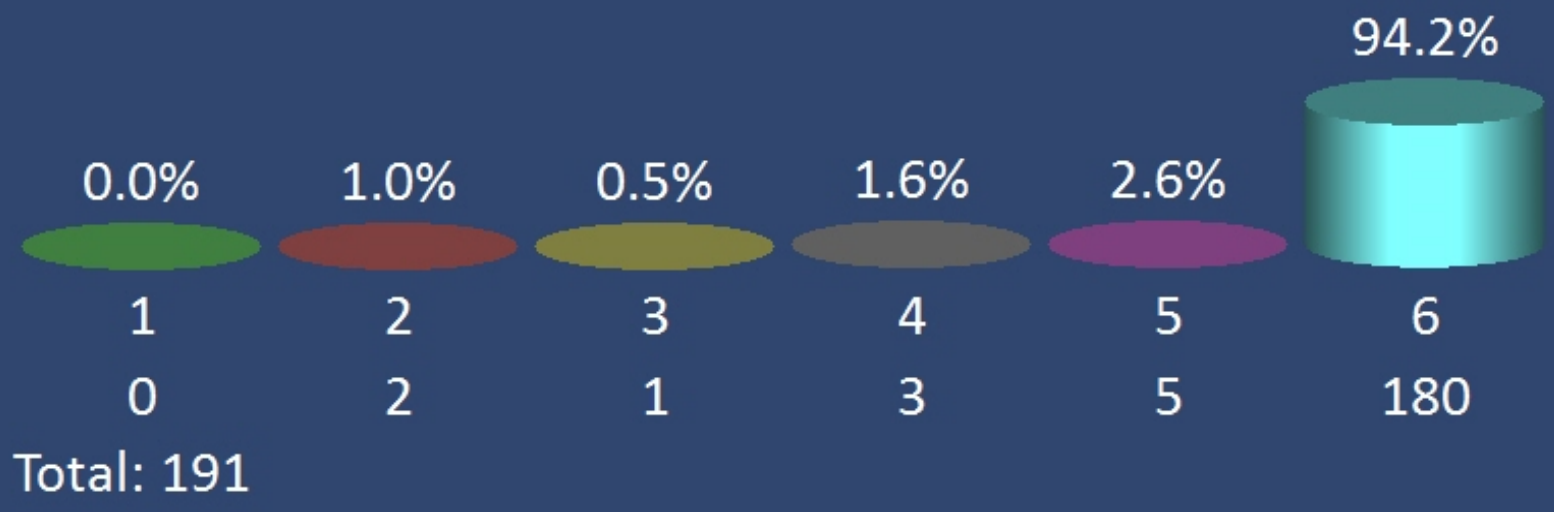
Case History

- 71 yo female in 3/08 developed persistent leukocytosis, frequent infection, and weight loss of ~ 5% body weight
- On exam noted to have splenomegaly (4 cm below costal margin)
- Marrow revealed primary myelofibrosis, JAK2 mutation present
- On initial referral to NMH: WBC 29.8 K/uL, hgb 13.1, plt 341
  - Neutrophils 85%, metamyelocytes 2%, nucleated RBCs 3%, lymphocytes 4%, monocytes 2%, basophils 6%

ARS Question

What factors are used to determine prognosis?

1. Age
2. Leukocyte count
3. Hemoglobin
4. Circulating blast percent
5. Constitutional symptoms
6. All of the above



DIPSS

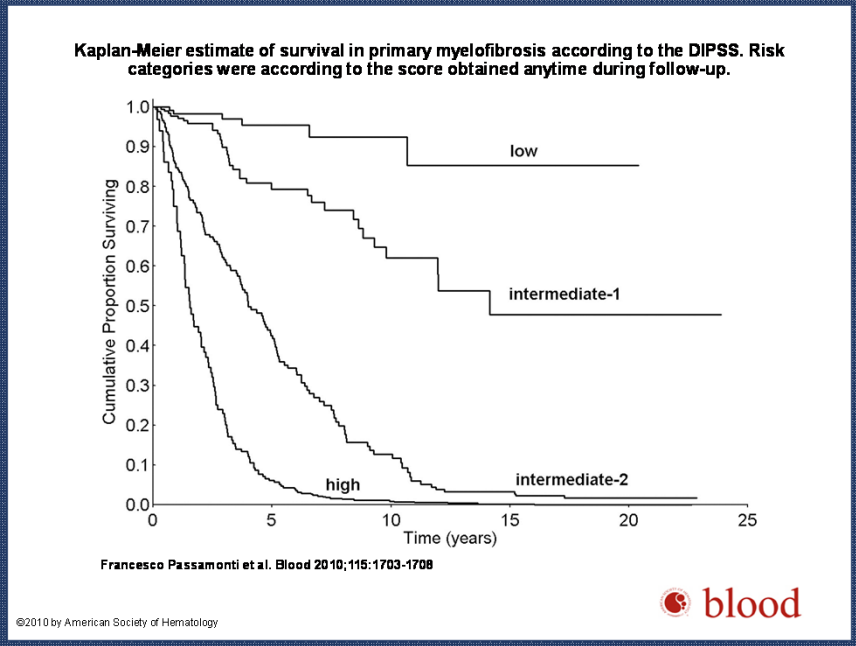
- Age >65 years – 1 point (pt)
- Leukocyte ct >25,000/microL – 1 pt
- Hemoglobin <10 g/dL – 2 pts
- Circulating blast cells ≥1% – 1 pt
- Constitutional symptoms – 1 pt

Subjects with 0, 1-2, 3-4, or 5-6 pts were low, int-1, int-2, or high risk, respectively

(Passamonti et al. 2010. Blood. 115(9): 1703)

DIPSS Plus – adds unfavorable karyotype, red cell transfusion need, and thrombocytopenia

(Gangat et al. 2011. JCO. 29(4): 392)



~ 1.5 years later (12/09)

- Progressive symptomatic splenomegaly and pruritus
- Exam now reveals that spleen is 21 cm below costal margin
- What would you offer her now?

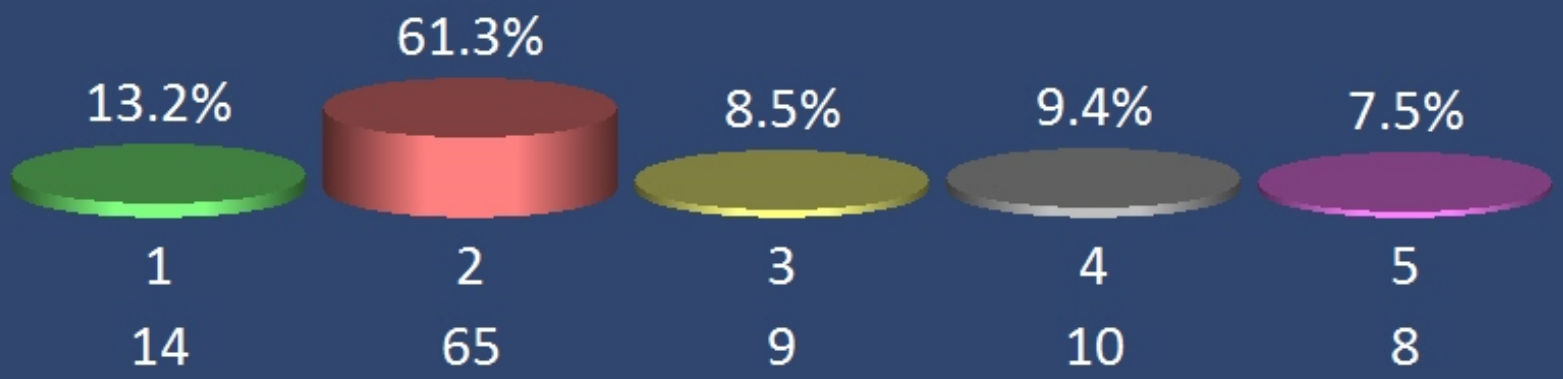
Her course

- Enrolled on randomized phase III trial of INCB 18424 vs placebo
- She had resolution of pruritus and noted improvement in weight and spleen decreased in size from 21 to 13.5 cm
- Maintained response until Summer 2012
- Course then complicated by varices and recurrence of symptomatic splenomegaly
- Now what?
  - Clinical trials offered to her but due to hyperbilirubinemia was not eligible

ARS Question

All of the following are true about JAK2 inhibitors except?

1. Ruxolitinib is the only agent commercially available and approved
2. Patients without a JAK2 mutation do not respond to JAK2 inhibitors
3. 28-42% of patients experience ≥35% spleen reduction with ruxolitinib
4. ~ Half of pts will maintain spleen volume reduction for 144 weeks with ruxolitinib
5. Anemia and thrombocytopenia occur with some frequency in patients treated with ruxolitinib



Total: 106

Cervantes et al. 2013. Blood. 122(25):4047

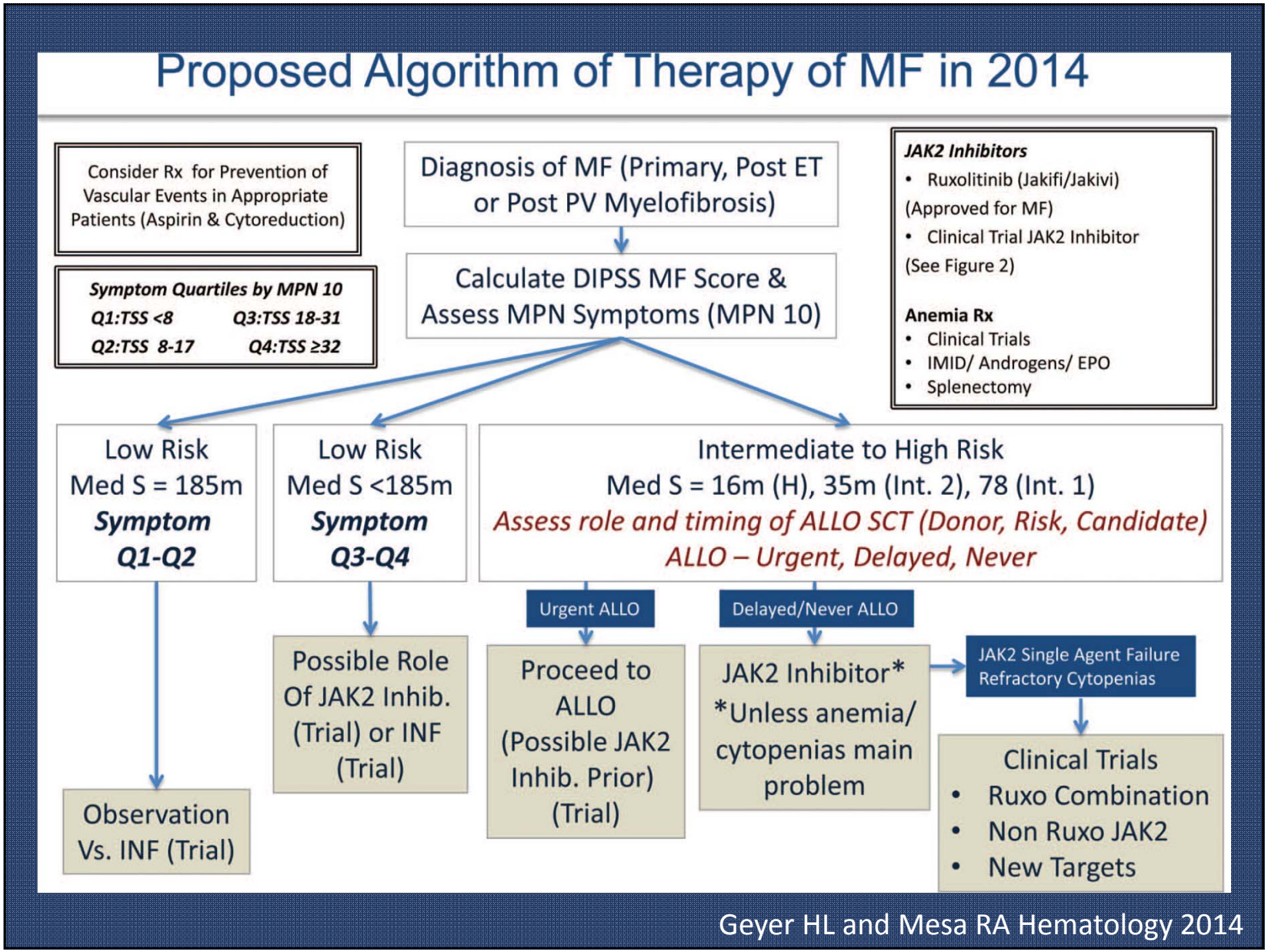
Ruxolitinib Follow up

- 3.5 year follow-up analysis of the COMFORT-II data, 42% reduction in risk of death compared with best-available therapy (BAT)
- At 3.5 years, the probability of survival was 54% and 71% in the BAT and ruxolitinib arms
- Ruxolitinib has also been shown to promote weight gain (96% of subjects) and to improve total cholesterol (97% of subjects) presumably via reversal of MF-related cachexia and catabolic pathways

Harrison CN et al. EHA 2014
Mesa RA et al. ASH 2012

Take Home Points

- AlloSCT decreases risk of leukemic transformation; but not appropriate for many patients
- Prognostic scoring systems
- Many agents utilized for palliation
- Ruxolitinib generally reserved for those with debilitating constitutional symptoms or severely symptomatic splenomegaly
- Many other JAK inhibitors and other agents being studied



References

- Passamonti F et al. DIPSS model. Blood 2010
- Cervantes F et al. 3 year results of COMFORT-II. Blood 2013
- Mesa R et al. PERSIST-1 ASCO 2015
- Harrison CN et al. EHA 2014
- Mesa RA et al. ASH 2012
- Geyer HL and Mesa RA Hematology 2014
- MPN Research Foundation
  - http://www.mpnresearchfoundation.org/Support-Groups

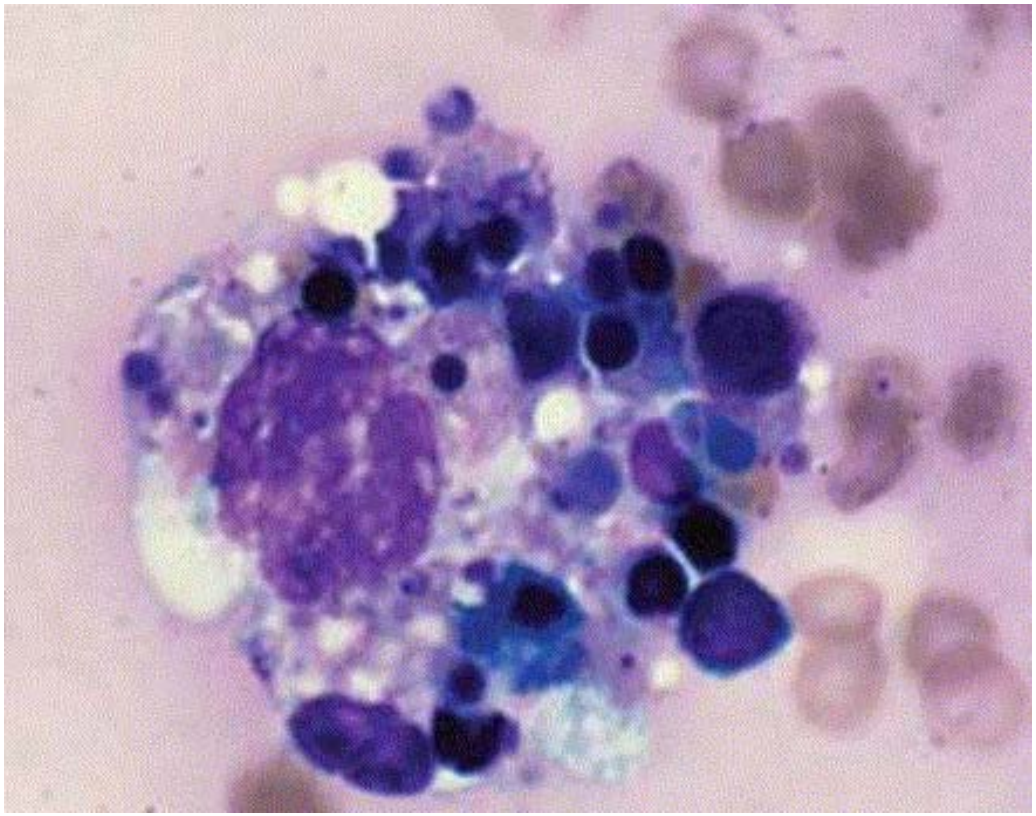
CASE 3

Joseph C. Alvarnas, MD
City of Hope Comprehensive Cancer Center

Patient Presentation

- The patient is a 23-year-old man who presented with epistaxis, hyperbilirubinemia, and pancytopenia
- The patient had multiple erythematous skin lesions and hepatosplenomegaly at presentation
- EBV PCR demonstrating 8200 copies/ml rising to 272,000 copies/ml
- Biopsy of skin lesions demonstrated presence of NK/T-cell non-Hodgkin lymphoma (gamma chain rearrangements)
- Marrow biopsies showed evidence of hemophagocytosis

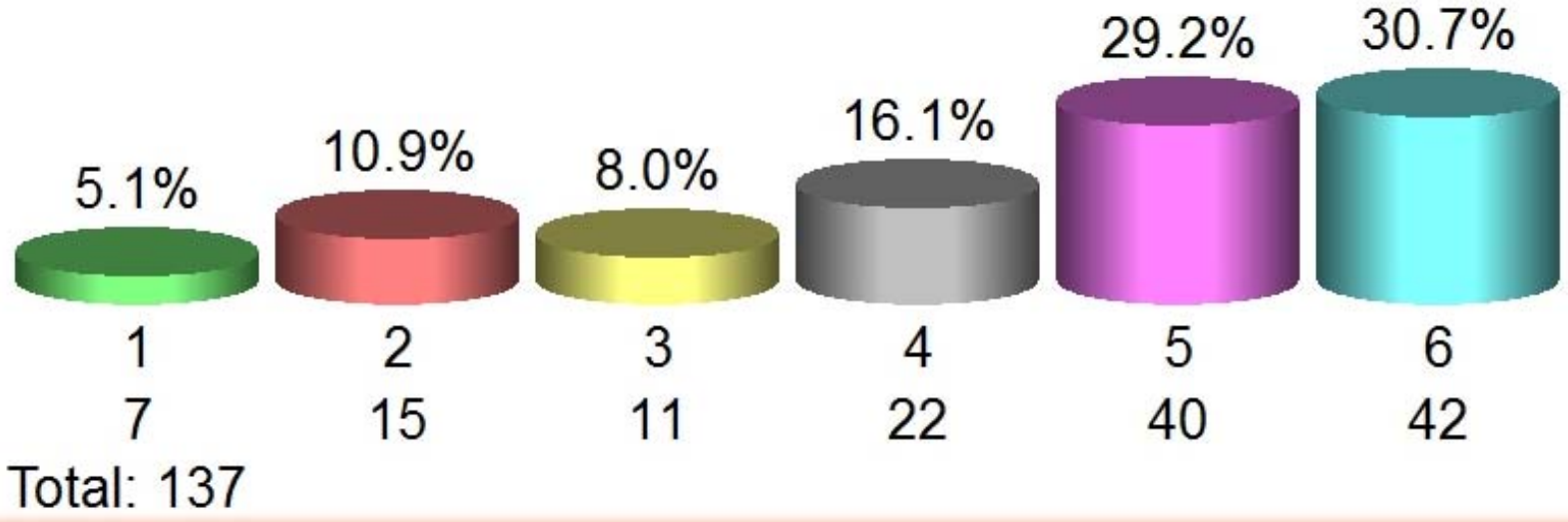
Patient Presentation



ARS Question

All of the following are criteria that are used to diagnose hemophagocytic syndromes EXCEPT:

1. Elevated liver enzymes
2. Fever ≥38.5ºC
3. Elevated soluble CD25
4. Hypertriglyceridemia
5. Elevated IFN
6. Elevated PT/PTT



Patient Presentation

- Patient treated with foscarnet, rituximab and then admitted for multi-agent chemotherapy
- The patient achieved a remission and subsequently underwent allogeneic stem cell transplantation
- 8 months post allogeneic transplant, the patient relapsed with progressive renal failure, anemia, cytopenia due to hemophagocytosis
- The patient died from progressive NHL

ARS Question

Which of the following statements is/are true about hemophagocytic syndromes?

1. They can be inherited or can occur sporadically in response to infections or other triggers
2. Patients should be treated with allogeneic HCT
3. There is a high mortality without treatment
4. The most common infectious cause is CMV
5. 1 and 3
6. All of the above

Total: 153

Hemophagocytic Syndromes

- Hemophagocytic lymphohistiocytosis (HLH)
- May occur as a primary disorder or secondary (sporadic forms) to a number of infections and malignancies
- Primary HLH may occur as familial syndromes[1]
    - FHLH1, FHLH2, FHLH3, FHLH4, FHLH5
        - HLH is only manifestation of disorder
    - Chediak-Higashi
    - Griscelli II
    - Hermansky-Pudlak II
    - X-linked lymphoproliferative disorders
    - X-linked severe combined immunodeficiency
    - X-linked hypogammaglobulinemia
- Most frequently diagnosed in pediatric population
- However, primary HLH may present at any age, from perinatal to 8th decade of life

1. Weitzman. Hematology (ASH Education Book). 2011:178

Triggers for Secondary HLH

Infection

- Epstein-Barr Virus (EBV) – most common infectious cause
- Cytomegalovirus (CMV)
- Parvovirus
- Herpes simplex virus (HSV)
- Varicella-zoster virus (VZV)
- Measles virus
- Human herpes virus-8 (HHV-8)
- H1N1 influenza virus
- Avian flu
- SARS
- HIV infections

Triggers for Secondary HLH

Immunological/Rheumatological Diseases – Macrophage Activation Syndrome (MAS)

- Adult onset Still's disease
- Systemic lupus erythematosus
- Rheumatoid arthritis
- Mixed connective tissue disease
- Sarcoidosis
- Systemic sclerosis
- Ankylosing spondylitis
- Sjogren's syndrome
- Dermatomyositis

Triggers for Secondary HLH

- Kawasaki disease
- Malignancies
  - Lymphoma
    - T/NK lymphomas
    - Anaplastic large cell lymphoma
  - Acute leukemia
    - Acute B-cell lymphoblastic leukemia
    - Acute myelogenous leukemia
  - Mediastinal germ cell tumors
  - Solid tumors

Signs/Symptoms of HLH

- Fever
- Jaundice
- Bleeding
- Neurological symptoms
  - Seizures
  - Encephalopathy
  - Ataxia
- Diarrhea
- Skin Rash
  - Edema
  - Purpura
  - Petechiae
  - Generalized rash
- Hepatosplenomegaly

Laboratory/Biopsy Findings

- Elevated liver enzymes
  - Hyperbilirubinemia
  - Transaminases
  - Increased GGT
- Hypertriglyceridemia
- Elevated PT/PTT
- Elevated creatinine/renal failure
- Elevated serum ferritin
- Elevated soluble CD25
- Hemophagocytosis on lymph node, liver, bone marrow biopsy

Diagnostic Criteria for HLH[1,2]

1. Detection of HLH-associated genetic lesion **OR**
2. Patient has 5 of the following:
   - Fever ≥ 38.5°C
   - Splenomegaly
   - Cytopenias affecting 2 out of 3 cell lines
     - Hgb < 9 gm/dL
     - Plt < 100,000/microL
     - Absolute neutrophil count < 1000/microL
   - Hypertriglyceridemia (fasting triglycerides >265 mg/dL) and/or hypofibrinogenemia (fibrinogen <150 mg/dL)
   - Hemophagocytosis in bone marrow, spleen, or lymph nodes
   - Low or absent NK cell activity
   - Ferritin > 500 ng/mL
   - Soluble CD25 > 2400 U/mL

1. Jordan and Filipovich. BMT. 2008;42:433
2. Weitzman. Hematology (ASH Education Book). 2011:178

Prognosis and Treatment of HLH

- HLH represents a state of profound immunological activation
  - Clinical manifestations reflect this state
- Delayed diagnosis worsens prognosis
- Patients often present with fulminant, multi-organ system involvement
- For patients with familial HLH, historical mortality up to 100%[1]
- Sole curative treatment for familial HLH is allogeneic transplant (HCT)
  - Allogeneic HCT survival rates > 70%[2]
  - 100-day post-HCT mortality up to 30%[2]

1. Jodan and Filipovich. BMT. 2008;42:433
2. Weitzman. Hematology (ASH Education Book). 2011:178

Prognosis and Treatment of HLH

- Mortality in secondary HLH exceeds 20%
- Treatment in secondary HLH based upon underlying disorder[1]
- MAS
  - High-dose corticosteroids
  - Cyclosporin
  - IV gammaglobulin
  - TNF-inhibiting agents
  - IL-1 inhibitors
  - Anti-IL-6 therapy
- EBV-related HLH
  - Rituximab
  - Chemotherapy
- Malignancy-associated HLH
  - Disease-related chemotherapy

1. Weitzman. Hematology (ASH Education Book). 2011:178

Take Home Messages on HLH

- HLH represents a series of primary and secondary disorders with fulminant presentation and multi-organ system involvement
- Diagnosis is based upon identification of specific genetic lesions or constellation of system findings of disease
- Mortality is high in untreated patients
- Delayed diagnosis increases risk of mortality
- Allogeneic HCT may cure patients with primary HLH
- Treatment of secondary HLH is directed toward reducing systemic inflammation and treating underlying disorder

NCCN Member Institutions