Myelodysplasia and Myelofibrosis

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Disclosures

- No shares
- No grants
- No speaking fees
- No advisory boards
- No dinners
- No soliciting
Outline

- An illustrative case
- What is myelodysplastic syndrome?
- Patient’s perspective: MDS as failure of bone marrow function
- Scientific perspective: MDS as a malignant disorder
- Prognosis
- Management
Case 1

- 72 y.o. man referred for evaluation of anemia
- WBC 2.9, Hgb 61, MCV 120, platelets 112
- Bone marrow biopsy:
  - Increased cellularity, megaloblastoid dyserythropoiesis, dysplasia in granulocytic and megakaryocytic series
  - Blasts 2%
  - Cytogenetics: 46,XY
- Diagnosis: Refractory anemia with multilineage dysplasia
- ‘Low-intermediate’ risk by IPSS score
Case 1

- No response to erythropoietin injections. Commenced on red cell transfusions.
- Developed progressive neutropenia and thrombocytopenia
- Over next 2 years received
  - 75 units PRBCs
  - 165 units platelets
- Continued to work full time as a janitor
Case 1

- 19 months after diagnosis, retired from his janitorial work
- At 20 months after diagnosis, was admitted to palliative care unit with *Staph. aureus* bacteremia, but recovered with antibiotics
- At 26 months, presented with headache, vomiting, and became obtunded. CT scan showed massive intracranial hemorrhage.
- Donated his body to medical science
Case 2

- 49 y.o. woman referred for evaluation of pancytopenia
- WBC 4.1, Hb 54, MCV 101.2, plts 64
- Bone marrow
  - Hypercellular with dysplasia of erythroid, granulocytic, and megakaryocytic lineages
  - 3.8% blasts
  - Karyotype 46,XX
Case 2

- Commenced on red cell transfusions
- Blood counts fell progressively; after 5 months:
  - ANC 0.4
  - platelets 15
- Started on erythropoietin + G-CSF
  - Platelets rose to 28 but petechiae worse
  - WBC 145
- epo/G-CSF discontinued
Case 2

- Considered for allogeneic stem cell transplant. Matched unrelated donor identified
- Transplant scheduled but delayed because donor exposed to infectious mononucleosis
- 10 months after Dx, while awaiting transplant, transformed abruptly to secondary AML
- Induction chemotherapy (×2 cycles) failed to induce remission
Case 3

- 79 y.o. woman noted to be pancytopenic on routine physical
  - WBC 1.93, ANC 0.57, Hb 113, MCV 105, and platelets 92
- Bone marrow
  - Decreased cellularity
  - No overt dysplasia of erythroid or myeloid lineages
  - 24.8% blasts
  - Cytogenetics normal
Response to azacitidine
Case 3

- Tolerated azacitidine well with only some constipation; continued very active lifestyle
- After 4 cycles of azacitidine, blood counts essentially normal and bone marrow showed complete remission
- Received total of 27 cycles of azacitidine but then developed progressive cytopenias
- Bone marrow showed relapse with 44% blasts
- Continues on supportive care
Questions

- Why did these patients have different courses?
  - what is the biology of myelodysplastic syndrome?
- Could we have predicted their outcomes
  - what are the prognostic factors and how is MDS classified?
- Could we have done better in their treatment?
  - what are the management options in MDS?
  - what does the future hold?
It’s all Greek to me

Myelodysplasia

“myelo” = marrow
“dys” = bad
“plasia” = appearance

Hence ‘bad-looking bone marrow’
Myelodysplastic syndrome (MDS) is a clonal disorder of hematopoietic progenitor cells characterized by impairment of effective hematopoiesis and by propensity to evolve to acute myeloid leukemia.
The Two Faces of MDS

- Bone marrow failure
- Pre-leukemia
MDS as bone marrow failure
Hematopoiesis

- Peripheral blood cells cannot divide and have limited life span
  - Red cells 100 days
  - Platelets 7 days
  - Neutrophils 6 hours
- Marrow must produce about 200 billion of each cell type each day to replace those that wear out
Hematopoiesis

Bone marrow

- CFU-GEMM
- BFU-E
- CFU-E
- CFU-Meg
- CFU-M
- CFU-GM
- CFU-Eo
- CFU-baso
- Lymphoid stem cell

Blood

- Red Cell
- Platelet
- Monocyte
- Eosinophil
- Basophil
- Neutrophil
- B-cell
- T-cell

Stem cell
Blood Count Thresholds

- **ANEMIA**
  - Symptoms typically become significant when Hb in 80s (regardless of sex)

- **NEUTROPENIA**
  - Concern of bacterial and fungal infection especially if ANC < 0.5 x 10⁹/L

- **THROMBOCYTOPENIA**
  - Risk of bleeding usually minimal unless platelets < 20-30 x 10⁹/L
  - >50 considered OK for minor surgery or anticoagulation, >80 for major surgery
Bone Marrow Failure in MDS

- All patients have cytopenias of one or more cell lines (red cells, white cells or platelets)
  - Anemia is usually the most prominent
- Low counts tend to get lower over time, but sometimes only over many years
- Improvement (without therapy) means the diagnosis was wrong or presages leukemia
Anemia Features

● Symptoms
  ▪ Exertional symptoms most sensitive
    ▪ Muscle fatigue, shortness of breath, pounding heart
  ▪ Orthostatic lightheadedness
  ▪ General tiredness (?)
  ▪ Ability to tolerate anemia is influenced by heart problems, lung disease, age, and how fast the hemoglobin level fell

● Findings
  ▪ Pulmonic flow murmur due to decreased blood viscosity, widened pulse pressure, lower BP
Neutropenia

- **Symptoms**
  - Mouth sores
  - Oropharyngeal and cutaneous infections
  - Susceptibility to infections (including abrupt and overwhelming blood stream infections)
Thrombocytopenia

● Symptoms
  ▪ Bruising
  ▪ Nose bleeds, gum bleeding, excessive menstrual bleeding

● Findings
  ▪ Petechiae, echymoses
  ▪ Mucosal purpura portends high risk of bleeding
Other symptoms

Some patients experience:

- Weight loss
- Fatigue that is unrelated to hemoglobin
- Fevers
- Night Sweats
- Splenomegaly
Management of low blood counts

- Transfusion
  - Red cells – typically every two to four weeks if production has failed completely
    - Transfusion is given depending on symptoms
    - Usually if Hgb less than 70-80g/L – but if marrow has failed, no point in waiting until symptoms are severe
    - Leads eventually to iron overload
  - Platelets – only if very low or if bleeding occurs
    - Transfusion generally used if less than 10
    - High risk of alloimmunization with repeated transfusion
  - White cells – can’t transfuse
Iron overload

- Each unit of blood transfused contains ~250mg of iron
- Toxicity begins to occur with ~10g excess body iron burden
  - Liver
  - Heart
  - Endocrine (pituitary, pancreas)
- Only low-risk transfusion-dependent patients likely to live long enough; no evidence to guide which patients warrant chelation therapy to reduce iron
Iron overload

- Working guideline (mine)
  - Ferritin >>1000
  - Liver iron on MRI >300
  - Elevated transaminases
  - Survival still expected >2yrs
- Deferoxamine 1g o.d. or b.i.d. by slow subcut injection (10ml)
- Deferasirox 30mg/kg p.o. daily
Management of cytopenias

- Growth factors
  - Erythropoietin can reduce or eliminate transfusion dependence in a minority of MDS pts
  - Generally effective only if serum epo level is <500
  - G-CSF (filgrastim, Neupogen) is occasionally used to boost white cells and may be synergistic with epo
  - Agonists of thrombopoietin receptor have been developed and are used in ITP (eltrombopag and romiplostim)
  - Use in MDS associated with rise in blast counts
Management of cytopenias

- Modify the underlying disease
  - Azacitidine
  - Lenalidomide
  - Bone marrow transplant
MDS as pre-leukemia
Mutations in MDS

- MDS is a clonal process
- Genome sequencing approaches show that about 5 mutations are present
- Some of these proteins regulate key events:
  - Proliferation (cell division)
  - Differentiation (development of mature cell with specific characteristics of the tissue)
  - Survival (prevention of apoptosis)
Clonal Evolution: MDS and AML
MDS mutations

- Recurring chromosomal alterations (e.g. trisomy 8, monosomy 7, del 5q)
- Single gene mutations including TET, IDH1, DNMT3a (all implicated in DNA methylation), RUNX1, N-ras, K-ras and p53
- Mutation profile overlaps AML but distinct genetic patterns
Genes in MDS

Xu et al., PNAS 2014; 111: 8589-8594
Altered Genes in Myelodysplasia

Ok et al., Leuk Res 2015;39:348-54
Who gets MDS?

- Risk strongly increases with age
- Risk is increased by exposures that can cause damage to DNA
  - Cancer chemotherapy, esp. alkylating/cross-linking agents
  - Radiation
  - Smoking
Two Faces of MDS

- Chronic hematopoietic failure
- Pre-leukemia

- Cases of MDS are heterogeneous, with different degrees of hematopoietic failure, and varying risk of progression to leukemia
- Because we can mostly manage the low counts (transfusion), the length of survival is determined largely by the risk of AML
A Spectrum

- MDS is viewed as a spectrum of disorders
- ‘low-risk’
  - milder cytopenias
  - little likelihood of leukemia
  - longer survival
- ‘high-risk’
  - more severe cytopenias, esp. neutropenia
  - high propensity to AML
  - shorter survival
The Spectrum of MDS

Refractory Anemia
Refractory Anemia with Ring Sideroblasts
Refractory Anemia with Multilineage Dysplasia
Refractory Anemia with Excess Blasts - 1
Refractory Anemia with Excess Blasts - 2
5q-syndrome
CMML-1
CMML-2
Determinants of risk

- Several risk score systems used
  - WHO, IPSS, R-IPSS
- Testing of the bone marrow is key to assessing risk
  - Blast count (number of immature cells)
    - If blasts >20% = AML
  - Chromosome analysis
  - Number of cytopenias
  - Need for transfusions
- Age also impacts survival
Greenberg et al., *Blood* 1997;89:2079
## IPSS

<table>
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<th>Blasts (%)</th>
<th>Karyotype</th>
<th># cytopenias</th>
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### Category

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## Cases 1 & 2

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**Category**

- Low
- **Int-1**
- Int-2
- High

**Score**

- 0
- **0.5 - 1.0**
- 1.5 - 2.0
- 2.5
Prognosis

Survival

A

percent

years

Low 267 pts
Int-1 314 pts
Int-2 179 pts
High 56 pts
## Case 3

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Prognosis – Case 3

Survival

![Graph showing survival rates for different groups (Low, Int-1, Int-2, High) with patient counts (267, 314, 179, 56) for each group.](image)
Risk-based management

- Low risk: Supportive care
  - Transfusions
  - Growth factors (erythropoietin +/- G-CSF)
  - Treatment of infections

- High risk: treatment like malignancy
  - Azacitidine
  - Lenalidomide
  - Bone marrow transplant
Azacitidine

- Inhibits DNA methylation
  - Presumed that some anti-oncogenes are silenced by aberrant methylation

- Approved for/proven benefit for survival in
  - Int-2 and high-risk MDS (per IPSS score)
  - CMML-2 with WBC < 13
  - AML with <30% blasts

- Median survival prolonged by 9mo compared to standard care
  - Benefit similar across all subgroups
Azacitidine: survival

Limitations of Azacitidine

- Cytopenias get worse initially
  - Often severe neutropenia
  - Infection risk surprisingly low
- Response takes up to 4 cycles (or longer)
  - Median 3 cycles
- Have to keep going as long as response persists
- Generally well tolerated but some side effects (constipation, injection site rxn)
- Unstable so must be administered immediately after pharmacist prepares it
Lenalidomide

- Specific benefit in rare MDS subtype (5q-syndrome)
  - Good prognosis anyway
  - Eliminates transfusion-dependence in most
  - Expensive
Bone marrow transplant

- Allogeneic BMT is only curative option in MDS

- Candidates
  - High-risk
  - Young
  - Fit
  - …rare
Summary

- MDS is a disease with two faces
- Shares much of the biology with AML, and survival strongly correlated with risk of evolution to AML
- Presentation is primarily with anemia, and anemia and need for transfusion dominate the burden of disease, while death is most commonly due to neutropenia or thrombocytopenia
- Both supportive care and chemotherapy are important in management, tailored to patients presentation and features
Questions?

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