

An Overview of the Myelodysplastic Syndromes

Stephen Couban

Director, Blood and Marrow Transplant Program

Halifax, Nova Scotia

October 24th, 2009

Important Disclaimers!

- An introduction to the myelodysplastic conditions
- My goal is to be as clear and accurate and up to date as possible
- What I say does not override the advice and recommendations of your doctors and healthcare teams
- Every person is different!

Overview

- What is myelodysplasia?
 - Classification systems
 - Causes
- How does myelodysplasia affect patients?
 - Signs and symptoms
- What happens to patients with myelodysplasia?
 - Prognosis
- Treatments
- Future Directions

What is myelodysplasia?

Healthy Bone Marrow

- Complicated and efficient factory for the production of blood:
 - White Cells
 - Fight infection
 - Mediate inflammation
 - Different types of white cells: neutrophils
 - Red Cells
 - Carry oxygen from the lungs to the heart and the rest of the body
 - Platelets
 - Key part of the body's clotting system

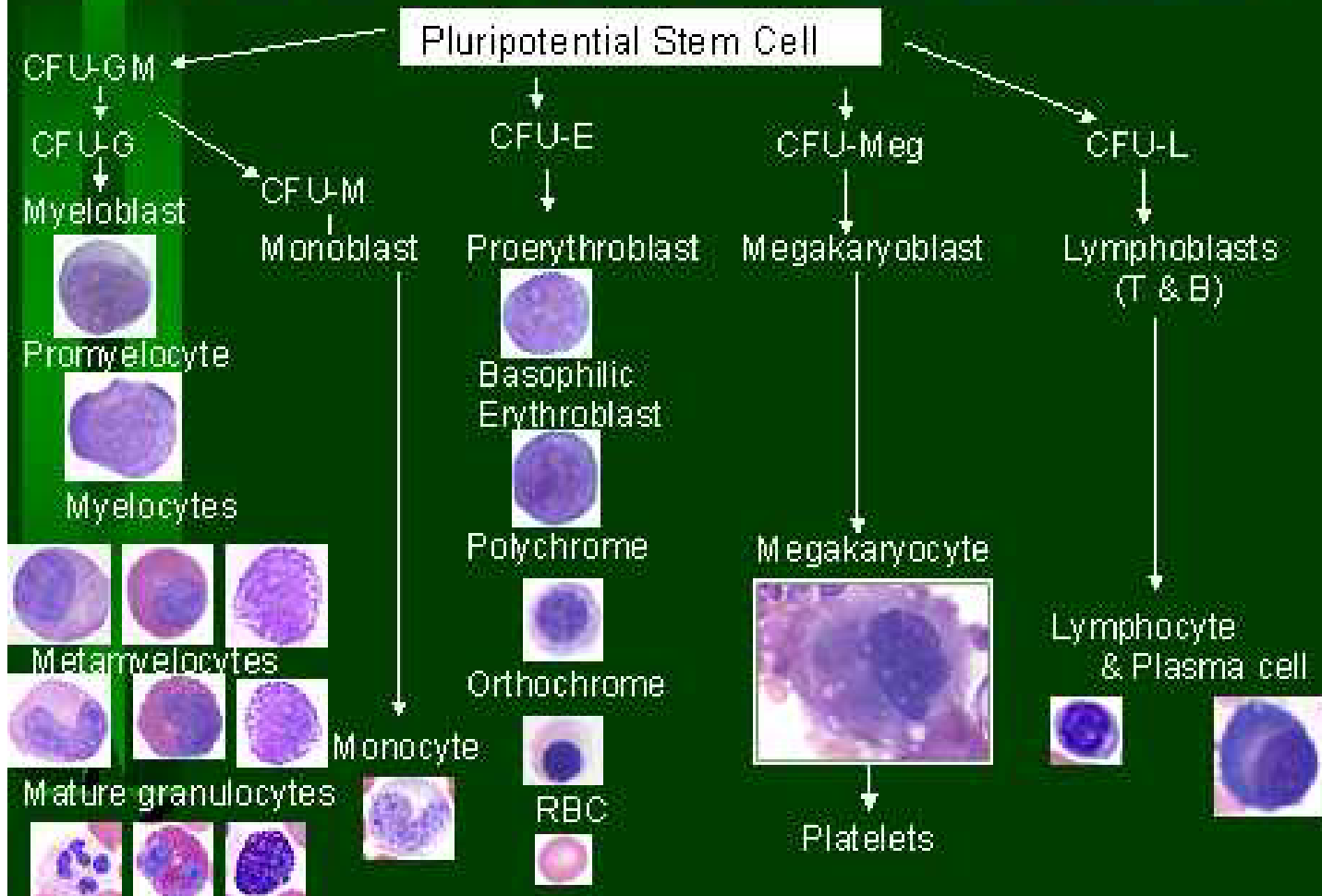
Bone Marrow (femur)





Healthy bone marrow

Development of RBCs, WBCs & Platelets



Myelodysplasia

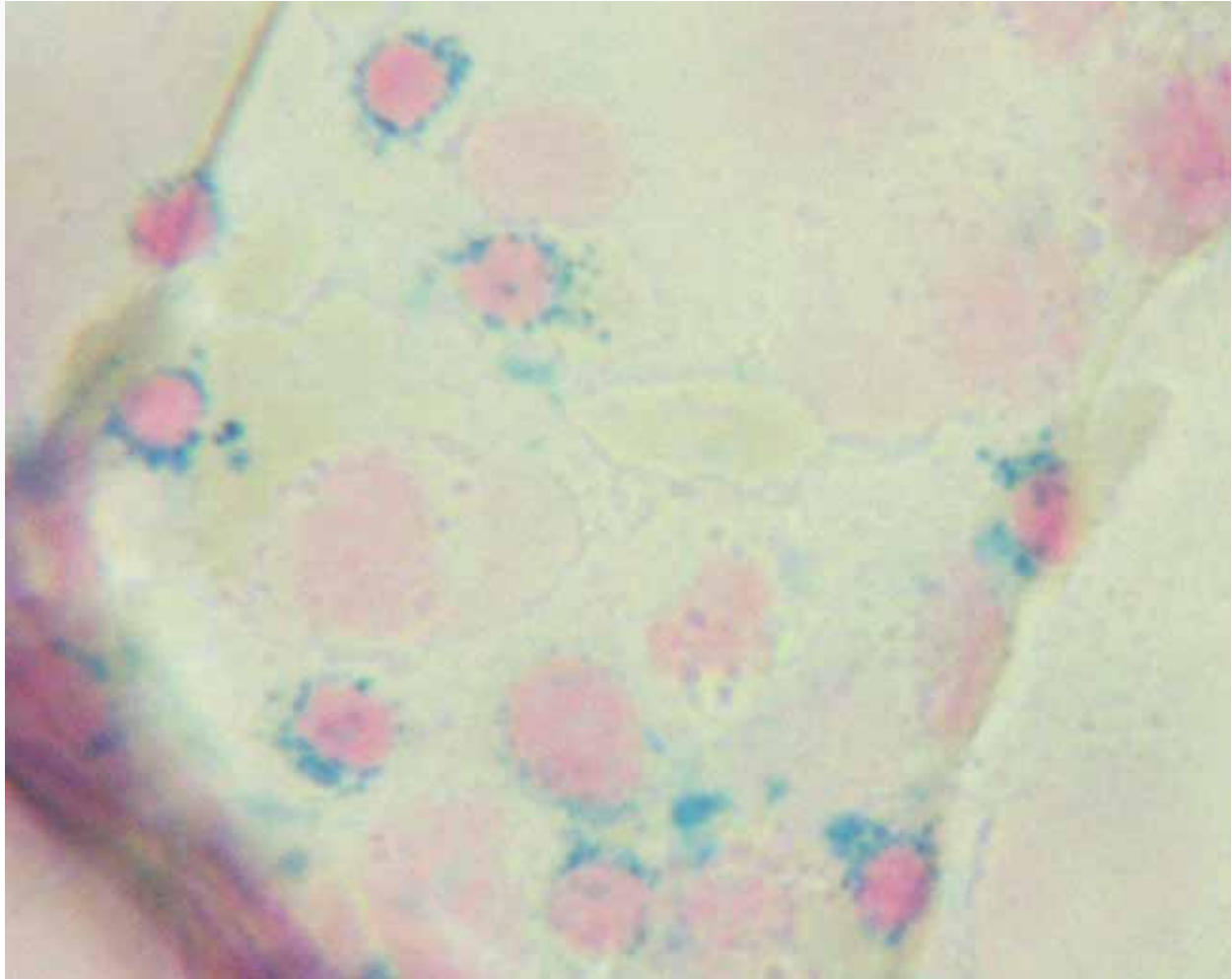
A Word about Terminology

- Myelodysplasia
- Myelodysplastic Syndrome
- MDS
- “Pre-leukemia”
- Myelodysplastic Neoplasms (MDN)
- Specific Names
 - Refractory Anemia
 - Refractory Anemia with ringed sideroblasts
 - Chronic myelomonocytic leukemia
 - A myelodysplastic syndrome not leukemia!
 - Refractory Anemia with excess blasts Type 1

Myelodysplasia

- Bone marrow does not function properly
- Car Engine Analogy: cylinders
- Wide range of findings and effects
 - Underproduction of cells
 - (Overproduction of cells)
 - Cells may be increased or decreased in number
 - May affect only one type of cells
 - Cells may be normal in number but not work properly

Ringed Sideroblasts



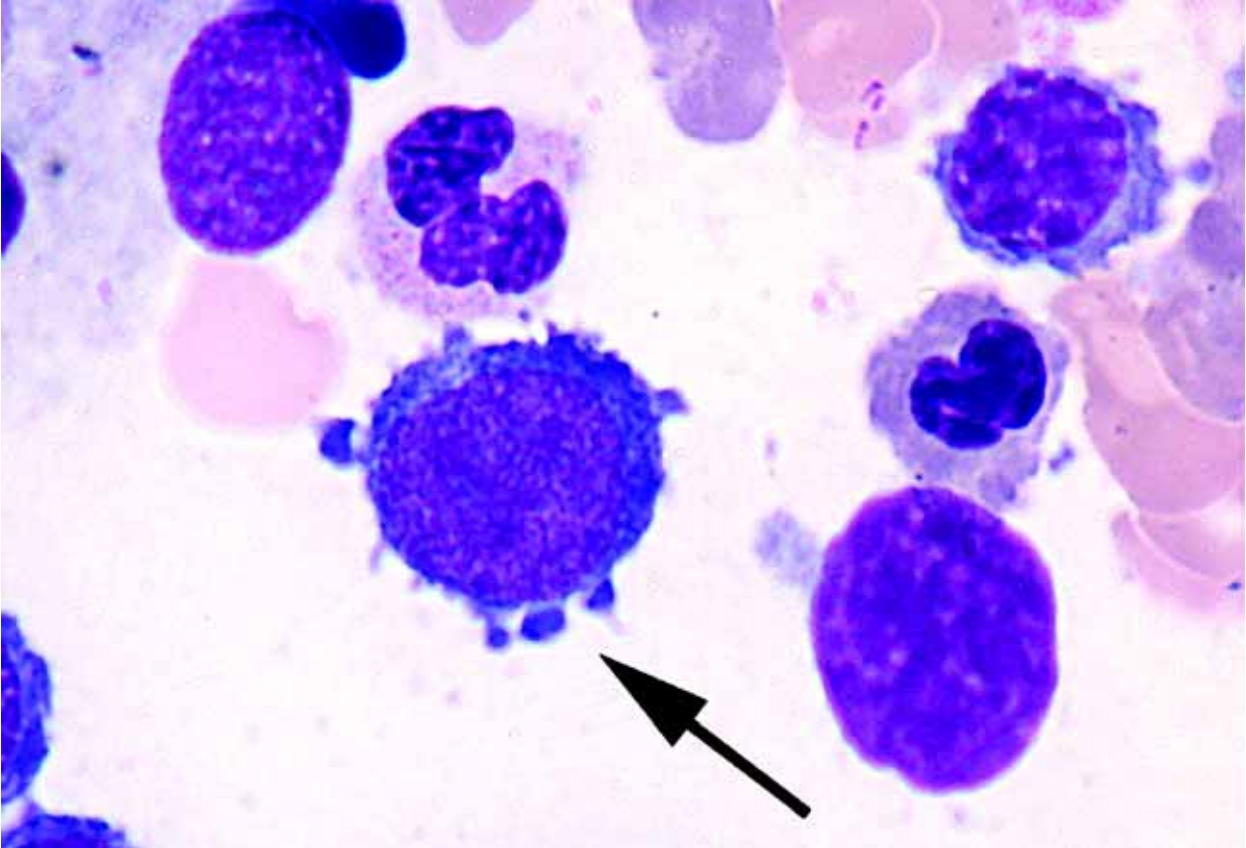
Lazarchick, J. ASH Image Bank 2008;2008:8-00114

Figure 1. This dysplastic granulocyte from a patient with MDS displays hyperlobulation of the nucleus



Maslak, P. ASH Image Bank 2004;2004:101193

Figure 2. Cytoplasmic budding



Maslak, P. ASH Image Bank 2006;2006:6-00037

Dysplasia

- One feature of MDS is dysplastic cells
 - Abnormal appearance of cells in the blood or bone marrow
- However, dysplasia can also be seen in other circumstances!
 - Infection, inflammation, deficiencies of some vitamins, lead poisoning

WHO Classification System

- Refractory Anemia
- Refractory Anemia with Ringed Sideroblasts
- Refractory cytopenia with multilineage dysplasia
- Refractory Anemia with Excess Blasts
 - RAEB-1: 5-9% blasts; RAEB-2: 10-19% blasts
- 5q Minus Syndrome
- Unclassified MDS

Heterogeneity=Variation

- Many different types of MDS
- In a particular patient, MDS may change over time

Causes of Myelodysplasia

- **Most often**
 - No known cause
- *Possible Specific Causes*
 - Radiation
 - Medications, especially previous chemotherapy
 - Chemicals: benzene
 - Very, very rarely: familial
- **Most patients are older than 65**
 - Younger people and rarely children can be affected

Symptoms and Signs

- Decreases or increases in cell counts
 - White cells, red cells, platelets
- Repeated infections
- Significant anemia
 - Fatigue, shortness of breath, paleness, requirement for blood transfusion
- Bleeding or easy bruising
- Pain due to an enlarged spleen

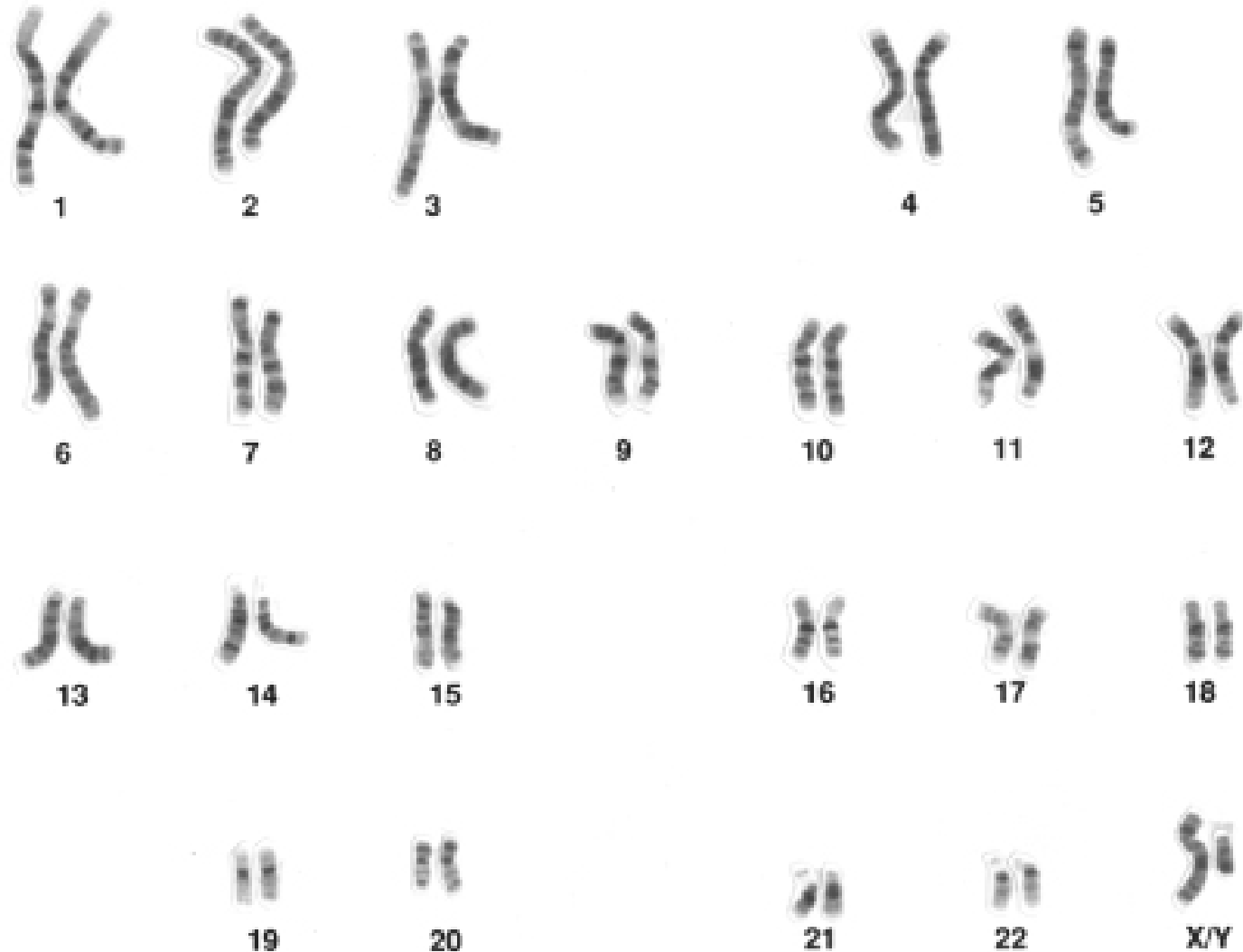
Signs and Symptoms

- Some patients have no symptoms!
 - Abnormal blood counts are noted when tests are done for another reason or as a routine

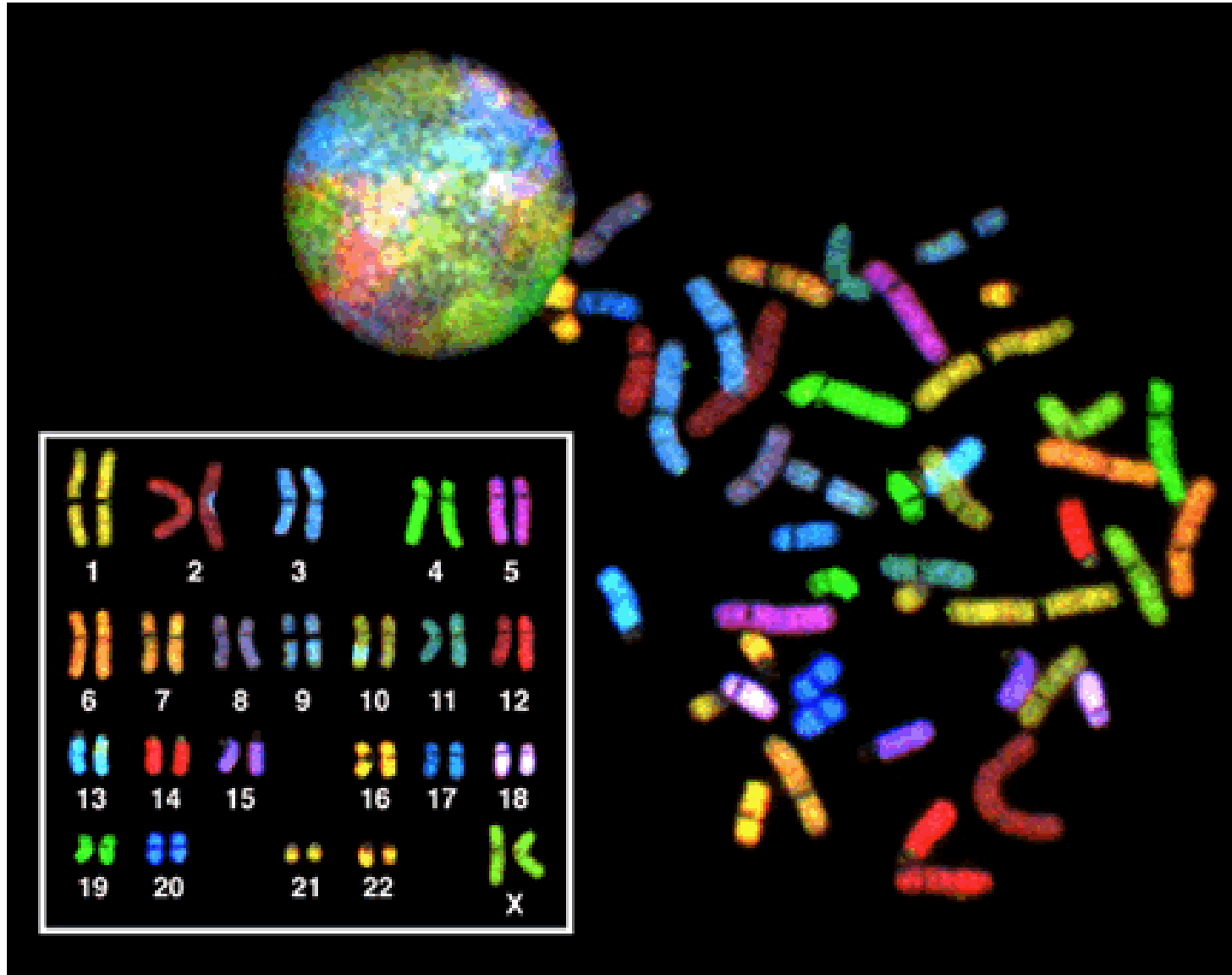
Diagnosis

- History and Physical Examination
- Complete blood count: “CBC”
- Peripheral Smear
 - CBC vs Peripheral Smear
- Bone Marrow Test
 - Bone marrow aspirate
 - Morphology
 - Flow cytometry
 - Cytogenetics
 - Bone marrow biopsy

Cytogenetics: Normal



Cytogenetics



Cytogenetics

46XY del 5, -7,-13,-18

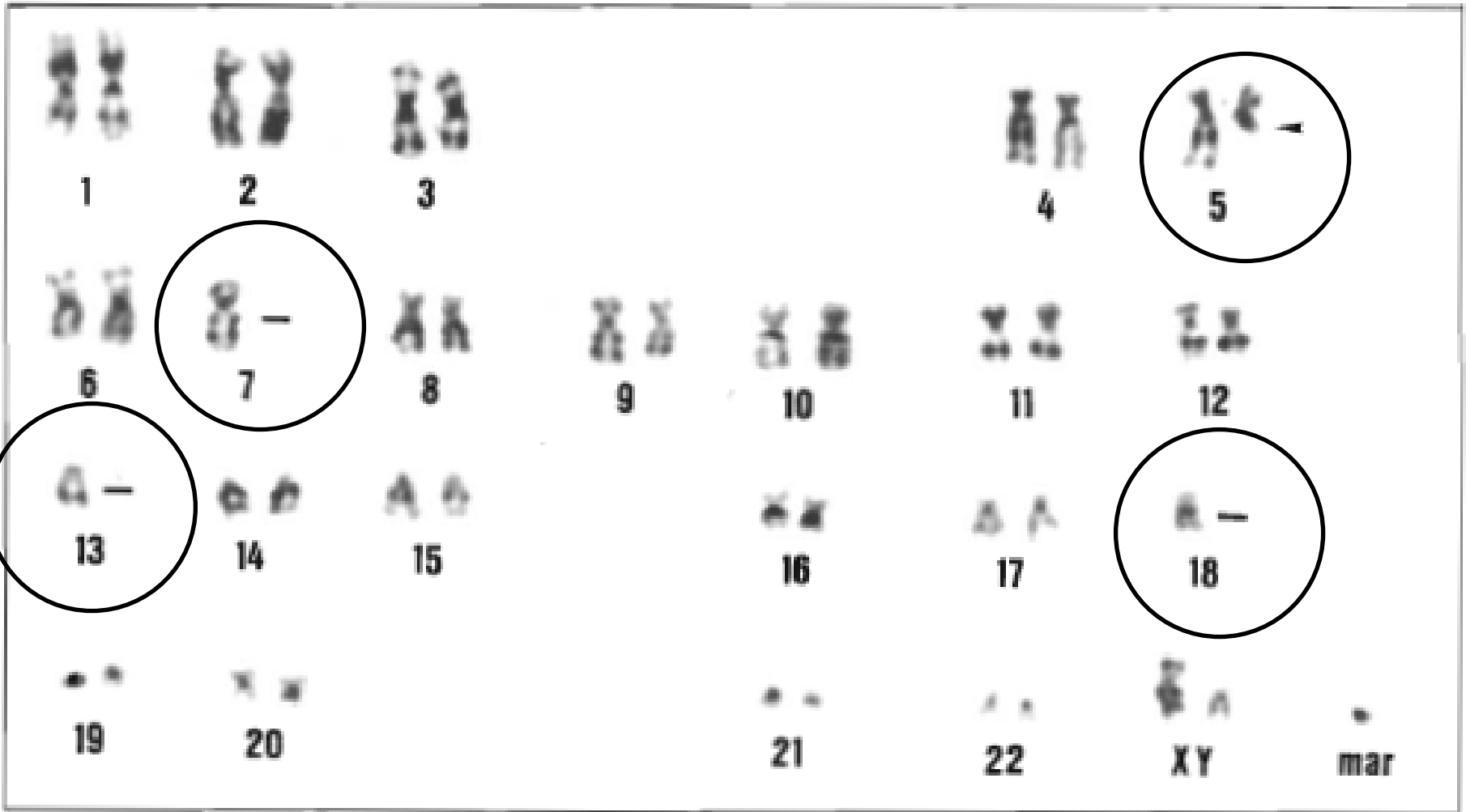


Figure 2 - G-banded karyotype of a bone marrow cell from patient 33 showing a complex karyotype: 44,XY,del(5)(q15),-7,-13,-18,+mar.

Diagnosis

- Sometimes, diagnosis is not straightforward!
 - No one single test
- Patient may need to be followed over time before diagnosis is clear
 - Important to avoid overdiagnosis and underdiagnosis
 - Eg:
 - Anemia of chronic disease vs MDS
 - Acute leukemia vs MDS
- About 30% of patients with MDS will progress to acute myeloid leukemia (AML)
 - Different risk depending on type of MDS and other factors

Prognosis

- Great variability in how patients with MDS fare over time
 - Some have the condition for many years with few or no problems
 - Others may become very ill quickly
- When first diagnosed with MDS, how can we tell how an individual person will fare?

Prognosis

blood

1997 89: 2079-2088

International Scoring System for Evaluating Prognosis in Myelodysplastic Syndromes

Peter Greenberg, Christopher Cox, Michelle M. LeBeau, Pierre Fenaux, Pierre Morel, Guillermo Sanz, Miguel Sanz, Teresa Vallespi, Terry Hamblin, David Oscier, Kazuma Ohyashiki, Keisuke Toyama, Carlo Aul, Ghulam Mufti and John Bennett

IPSS

Prognosis

Table 3. IPSS for MDS: Survival and AML Evolution

| Prognostic Variable | Score Value | | | | |
|---------------------|-------------|--------------|------|-------|-------|
| | 0 | 0.5 | 1.0 | 1.5 | 2.0 |
| BM blasts (%) | <5 | 5-10 | — | 11-20 | 21-30 |
| Karyotype* | Good | Intermediate | Poor | | |
| Cytopenias | 0/1 | 2/3 | | | |

Scores for risk groups are as follows: Low, 0; INT-1, 0.5-1.0; INT-2, 1.5-2.0; and High, ≥ 2.5 .

* Good, normal, $-Y$, $\text{del}(5q)$, $\text{del}(20q)$; Poor, complex (≥ 3 abnormalities) or chromosome 7 anomalies; Intermediate, other abnormalities.

Treatment

Goals of Treatment

- Prolonging survival
- Improving quality of life

- Improving anemia
- Controlling infections
- Controlling excessive bruising and bleeding

Watchful Waiting and Supportive Care

- Regular bloodwork
- Treatment of infections
 - Immunizations, good dental care
- Treatment of anemia
 - Transfusions of red cells
- Treatment of bleeding
 - Transfusions of platelets
 - Medications to reduce bleeding
 - Fibrinolytic inhibitors, BCP

Growth Factors

- G-CSF or PEG-G-CSF (Neulasta)
- Erythropoietin Stimulating Agents
 - Erythropoietin, Darbopoietin
- Platelet Stimulating Agents
 - Clinical studies
 - Romiplostin, Eltrombopag
- Combinations of Growth Factors:
 - G-CSF+Epo

Blood and Marrow Transplantation

- Bone marrow replacement strategy
- Important to consider
 - Disease-specific factors: type of MDS
 - Patient-specific factors: other illnesses, type of match
- Different types of transplant
 - Sibling/related allogeneic transplant
 - Volunteer unrelated allogeneic transplant
 - Reduced intensity/Non-myeloablative transplant
 - “mini-transplant”

Blood and Marrow Transplantation

- Approximately 1/3 patients who receive an allogeneic transplant for MDS are cured
 - Highly and carefully selected patients
- BUT, only about 8% of all patients with MDS are able to have this treatment and have a donor

Specific Treatments

- Pyridoxine (Vitamin B6)
 - Sideroblastic Anemia
- Hypomethylating Agents
 - 5-Azacytidine (Vidaza)
 - Decitabine (Dacogen)
- Lenalidomide (Revlimid)
- Anti-thymocyte globulin(ATG) with or without cyclosporin

Hypomethylating Agents

- 5-Azacytidine (Vidaza)
 - Subcutaneous or iv injection once a day for 7 days every 4 weeks
 - Reduction in transfusion requirements
 - Decrease in blasts
 - Longer time to progression to AML
 - 5 –day schedule under study
- Decitabine
 - Continuous IV infusion
 - 17% of patients in a trial of 170 patients responded to decitabine
 - Transfusion independence
 - Longer time to progression to AML
 - Other dosing is understudy
 - Shorter daily infusion

5-Azacytidine: Vidaza

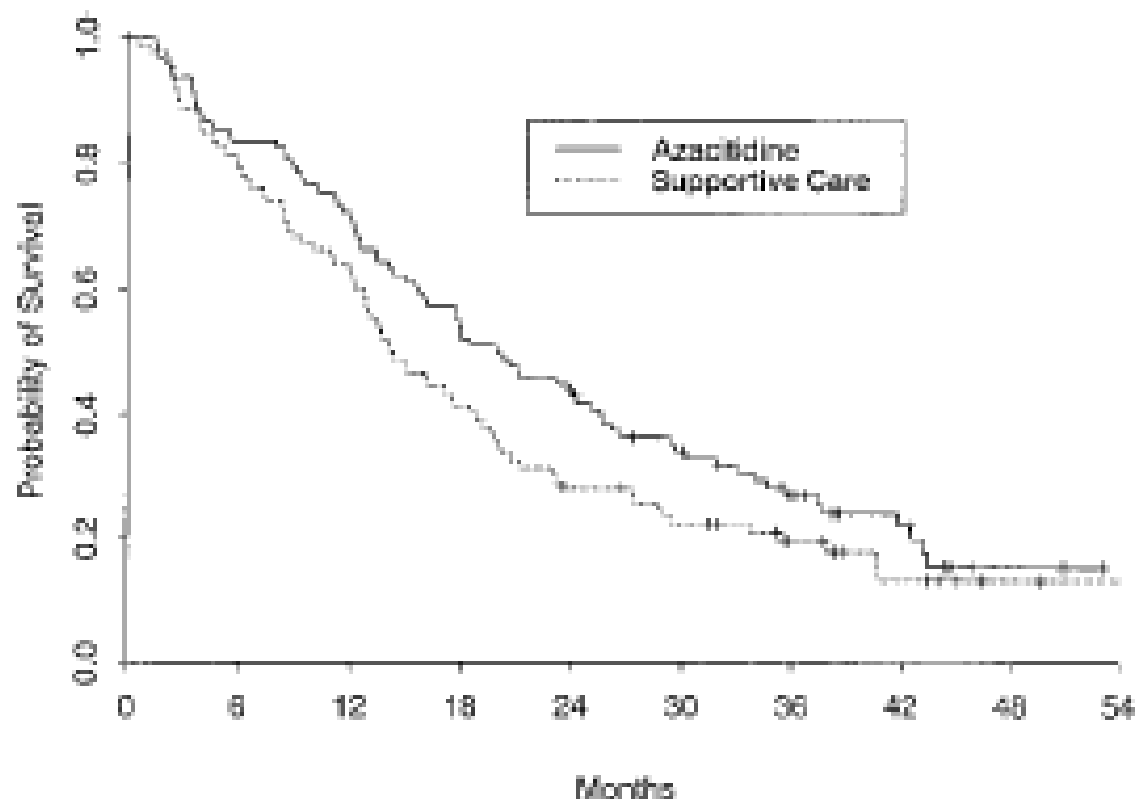
- Silverman et al, JCO 2002
 - 191 patients
 - If low grade MDS (RA, RARS), had to have additional reasons to treat
 - Standard arm:
 - best supportive care
 - Experimental group:
 - best supportive care + 5-aza-cytidine 75mg/m²/d sc for 7 days every 28 days
 - Number of treatments depended on response

5-Azacytidine: Vidaza

- Results
 - Median age: 68 (31-92)
 - Standard Arm
 - 5% patients had rise in counts
 - Time to AML or death: 12 months
 - Median overall survival: 14 months
 - Experimental Arm
 - 60% patients responded
 - 7% CR
 - Time to AML or death: 21 months
 - Median overall survival: 20 months
 - Side effects: low counts

AZACITIDINE IN MDS

Cross Over



Number of Patients at Risk

| | 0 | 6 | 12 | 18 | 24 | 30 | 36 | 42 | 48 | 54 |
|-------------|----|----|----|----|----|----|----|----|----|----|
| Azacitidine | 99 | 82 | 71 | 52 | 42 | 30 | 21 | 11 | 2 | 0 |
| Observation | 92 | 73 | 58 | 38 | 25 | 19 | 12 | 6 | 2 | 1 |

Fig 5. Overall survival by randomized arm and estimated according to the Kaplan-Meier method. Patients who were initially in the supportive care group and crossed over to treatment with azacitidine are included in the supportive care group in this plot.

Lenalidomide

- 5q minus Syndrome and anemia
 - Lenalidomide 10mg orally once a day
 - 2/3 patients who were red-cell dependant became transfusion independent
 - 9% had a 50% reduction in transfusion requirements
 - Almost 50% had a complete cytogenetic response
- MDS without 5q minus Syndrome
 - Reduction in transfusion requirements in 43%
 - Elimination of transfusion requirements in 26%

Lenalidomide

- My view:
 - Lenalidomide is a promising treatment for those with MDS affecting mostly the red cells
 - Particularly for those with low-risk MDS
 - Definitely for patients with 5q minus syndrome
 - Need more studies in larger groups of patients

Specific Treatments

- Iron Chelation

Summary

- A group of blood disorders with a wide spectrum of signs and symptoms
 - Infection, anemia, bleeding
- Very variable course
 - Some patients can live with this condition for many years without requiring treatment
 - Others need treatment urgently
- Treatments
 - Promising new treatments

Thank you!