

Myelodysplastic Syndromes

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Scheme

- Terminology and History
- Incidence
- Blood cell production
- Symptoms
- Diagnostic tests
- Therapeutic options
- Survey of patients
- Conclusion



MDS-Definition

- A heterogenous clonal disorder derived from an abnormal multipotent progenitor cell.
- It is characterised by hyperproliferative bone marrow, dysplasia, ineffective haematopoiesis leading to cytopenias.

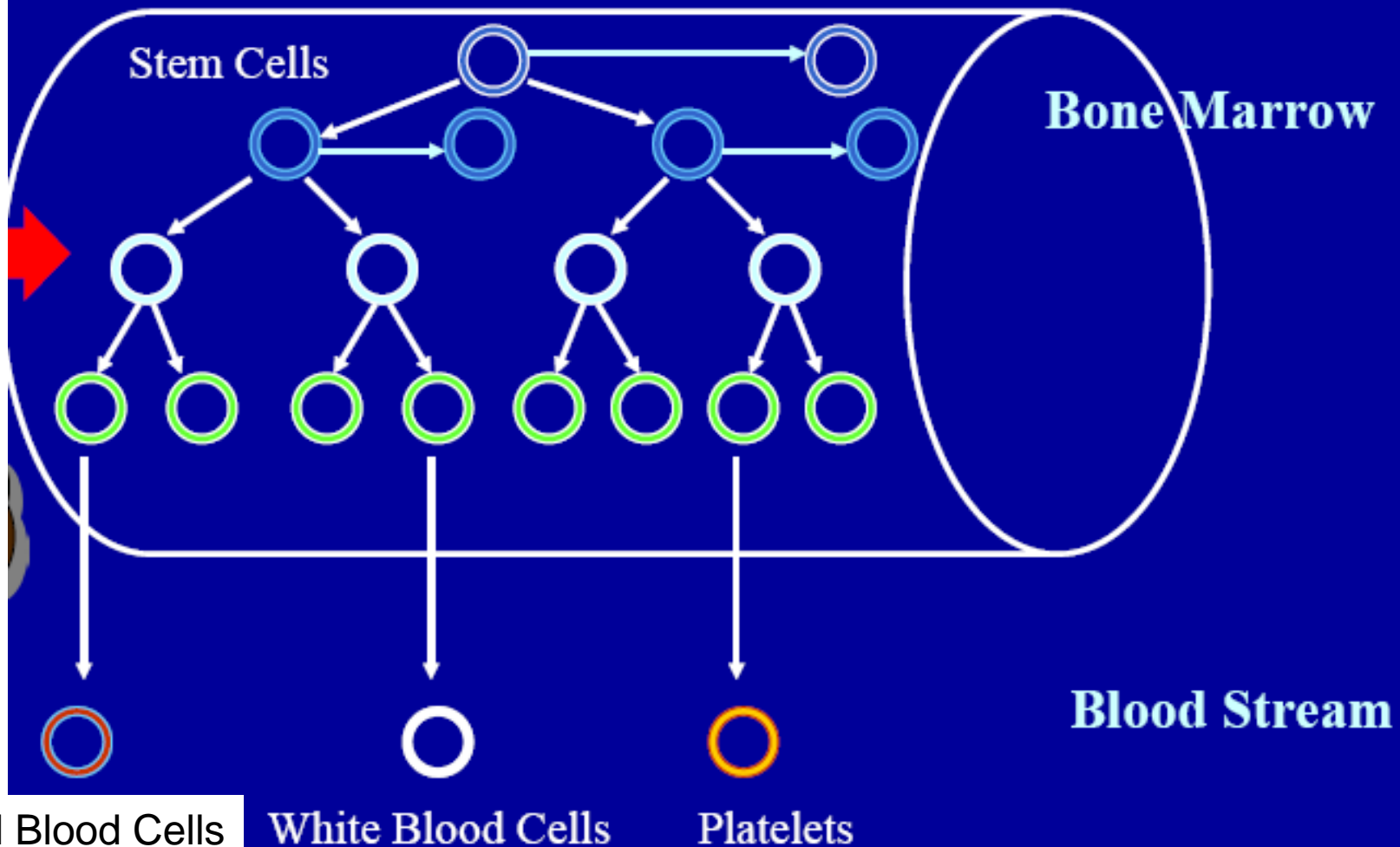
What does the term "myelodysplastic" actually mean?

- **Myelo** = marrow
- **Dysplastic** = abnormal or just gone bad or funny looking

Bone marrow cells fail to make enough healthy blood cells- quantity and quality is affected.

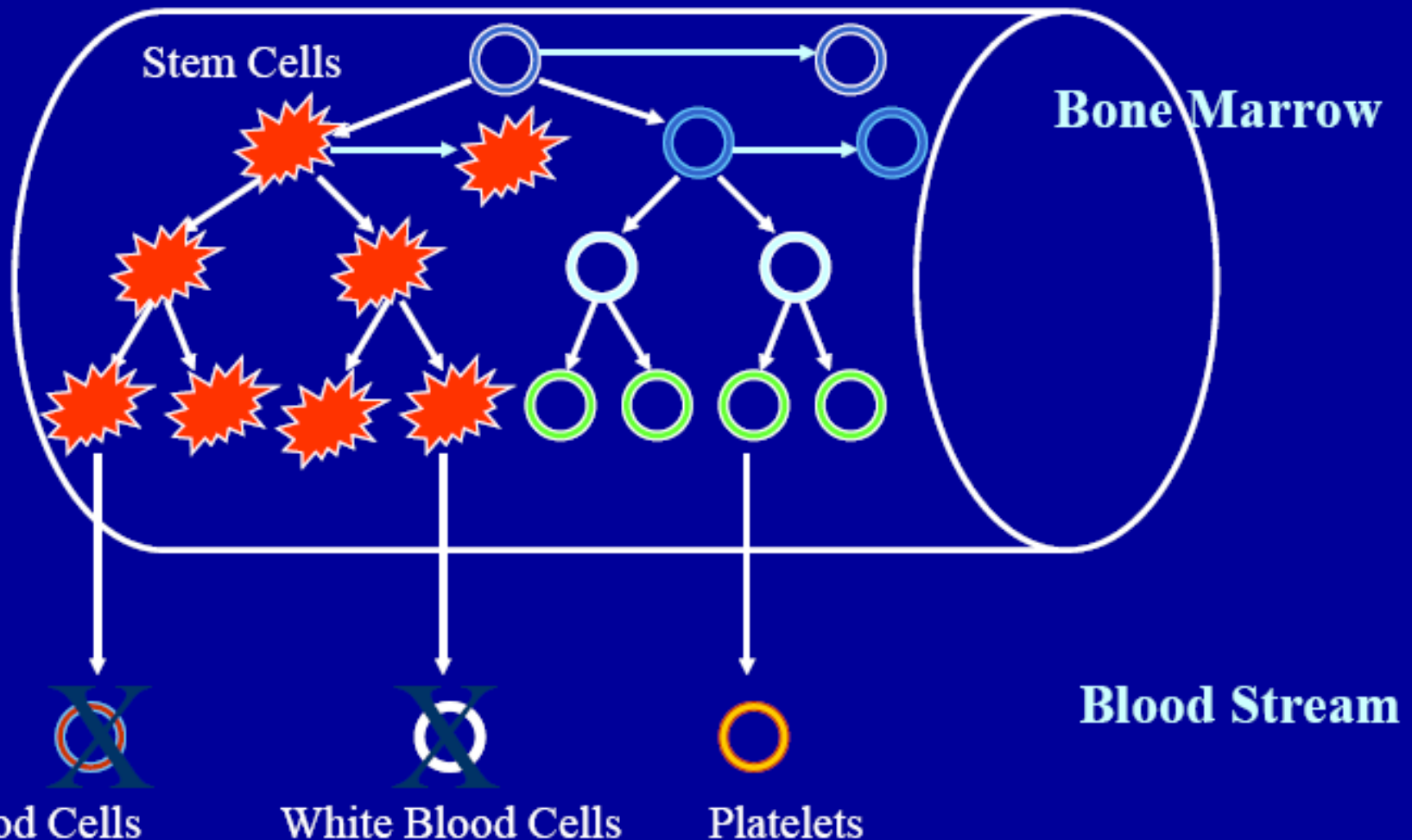
- Crowding out remaining normal cells
(Cancer)

Bone Marrow Basics



Red Blood Cells
20 trillion

MDS in the Bone Marrow (II)



MDS features

All people with MDS have two things in common

- Low count for at least 1 blood cell type (cytopenia)
- Bone marrow and blood contain blood cells with an abnormal shape, size, or look.

Symptoms of MDS

Asymptomatic – abnormal blood count

Fatigue, lack of energy and shortness of breath
- caused by anaemia (low red cells)

Bruising and bleeding
- caused by low platelet cell count

Infection
- due to low numbers and/or poorly functioning white cells

Patients



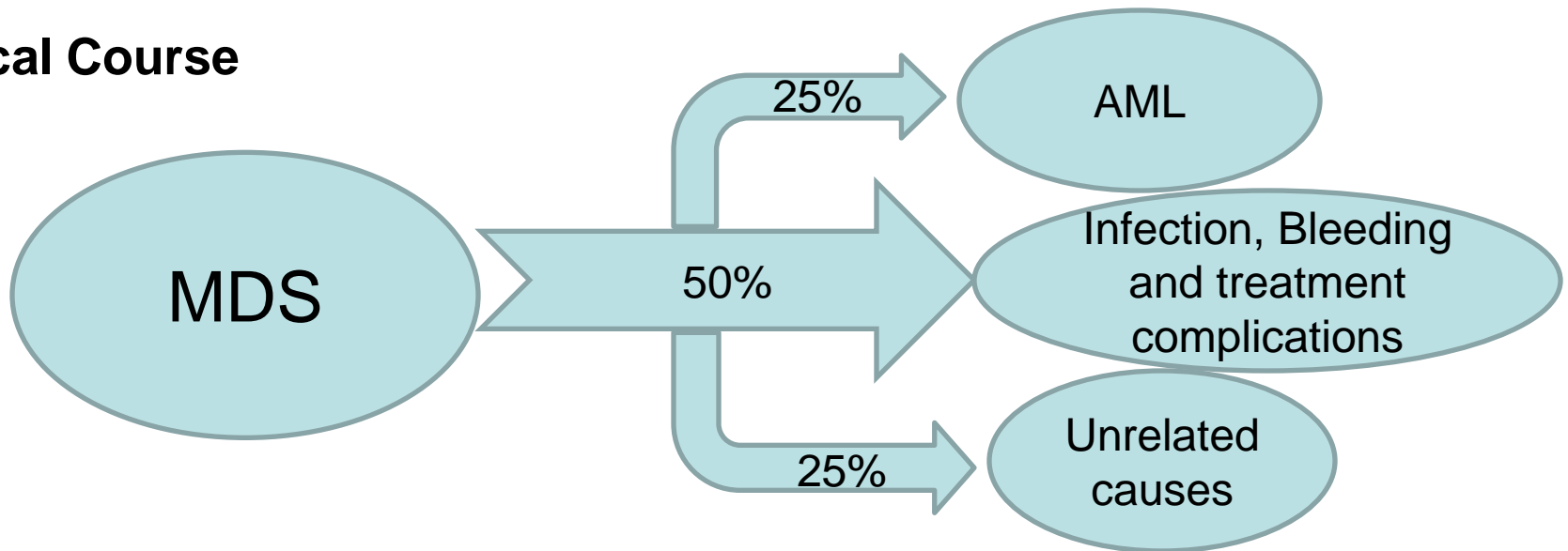
Median age is @
72 years

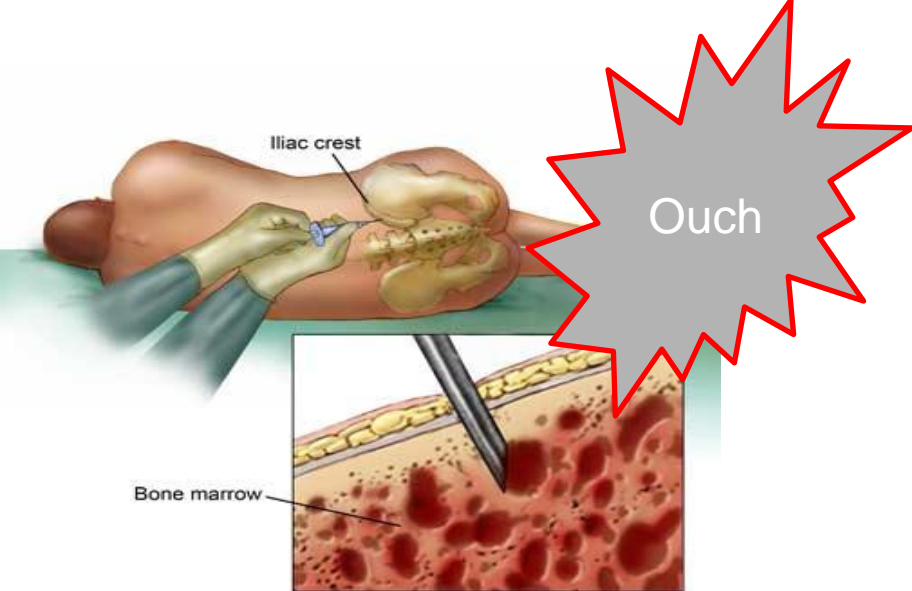


Prior exposure to chemo and
or radiotherapy, but 90% do
not have any known exposures



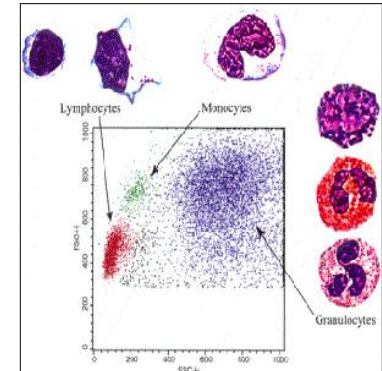
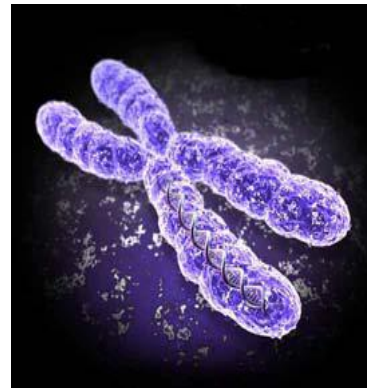
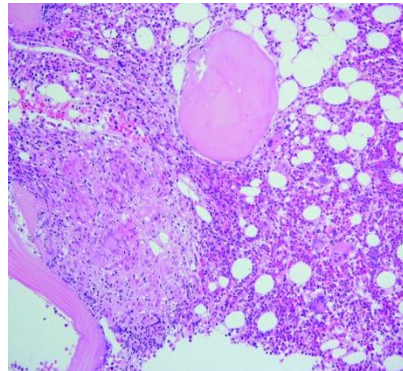
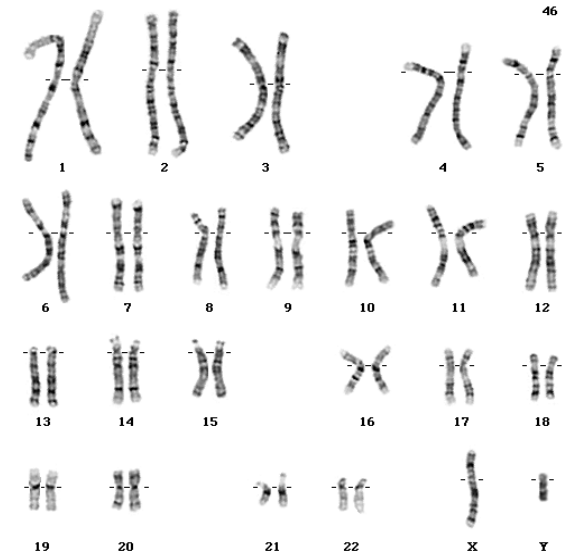
Clinical Course





Bone marrow aspirate
and trephine

Diagnostic Tests



Blood film/Aspirate

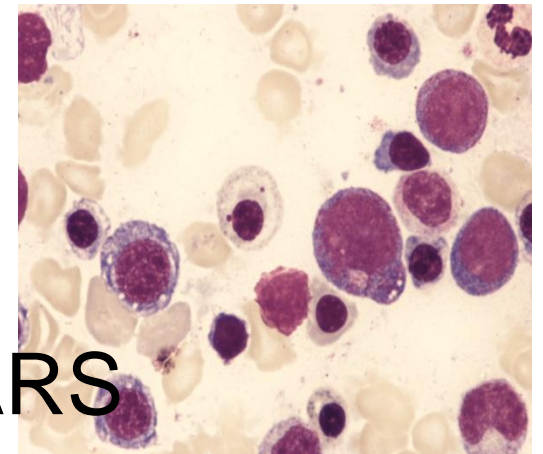
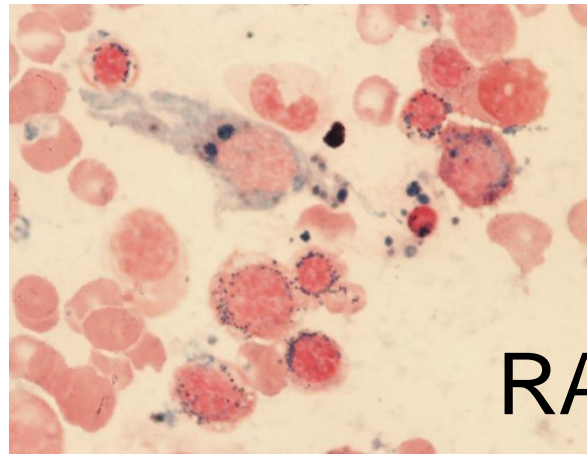
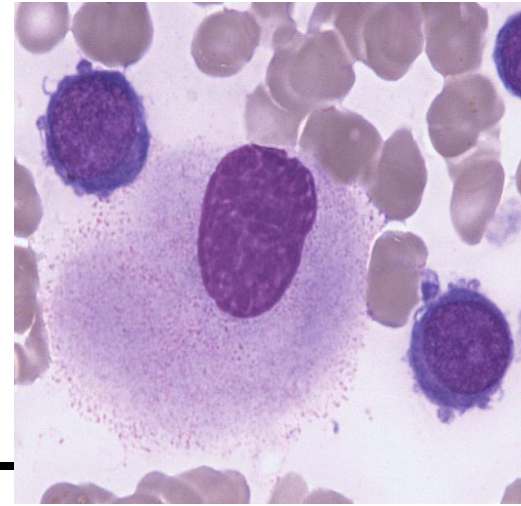
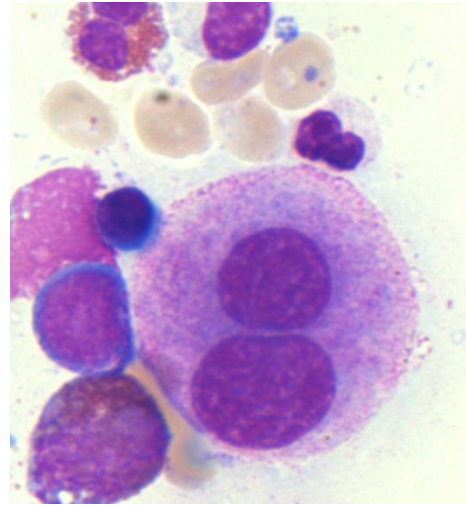
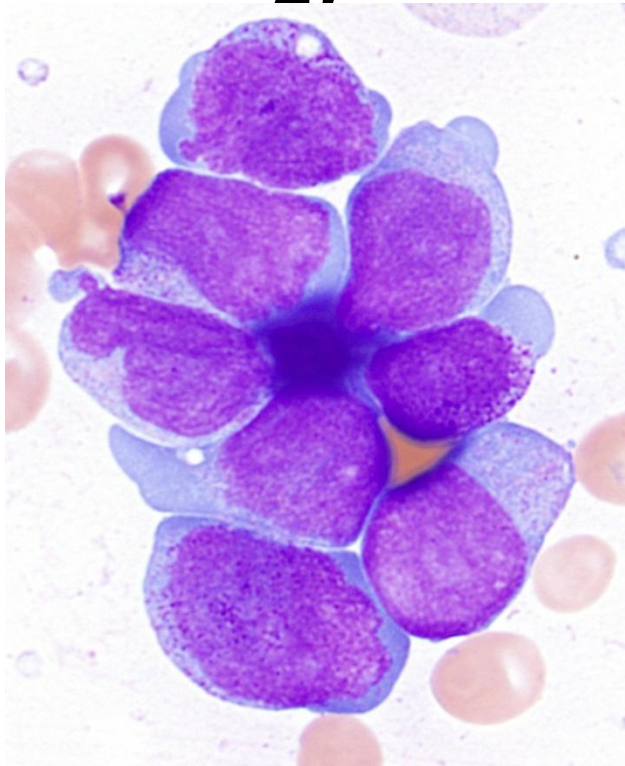
Trephine

Cytogenetics

Flow Cytometry

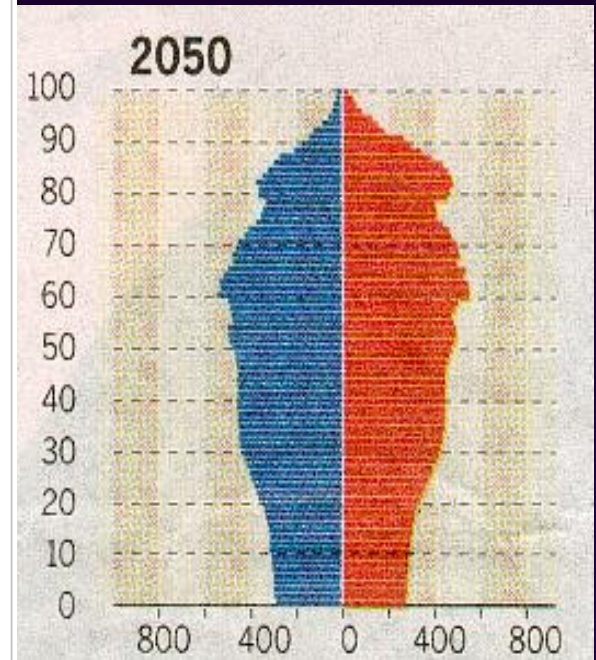
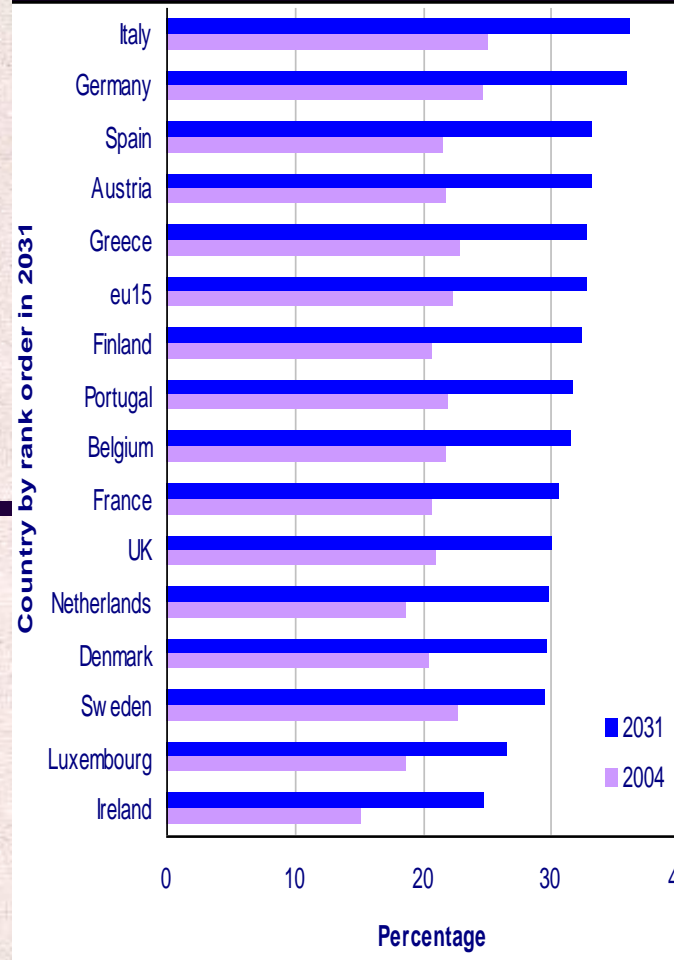
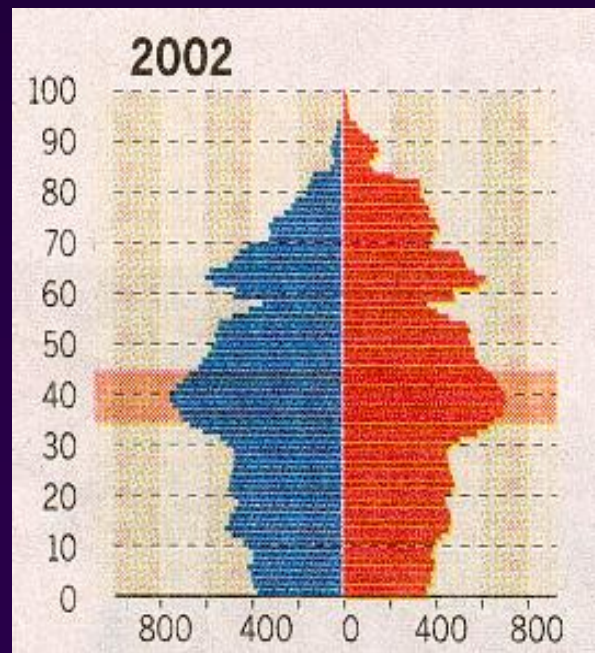
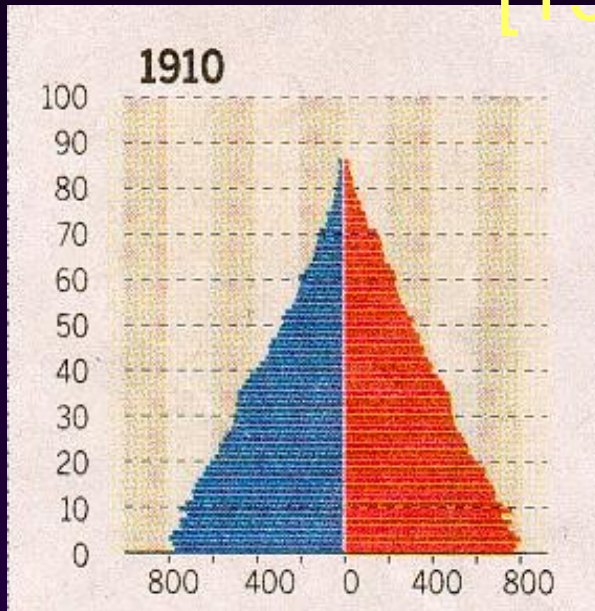
Morphology of MDS

Blasts (Type 1 and 2)



RARS

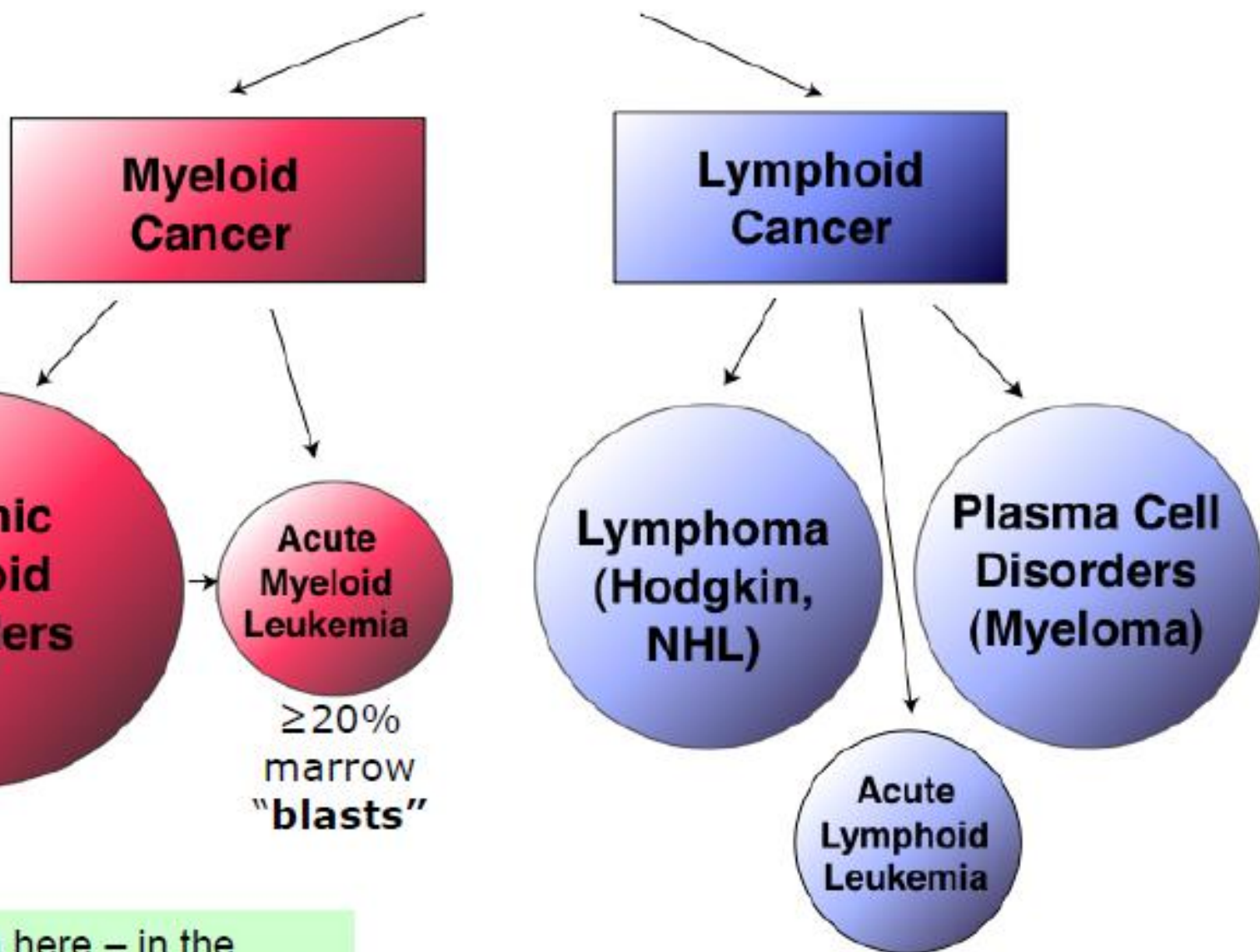
Demographics of Germany [1910 – 2050] and Europe



Statistisches Bundesamt, 2002

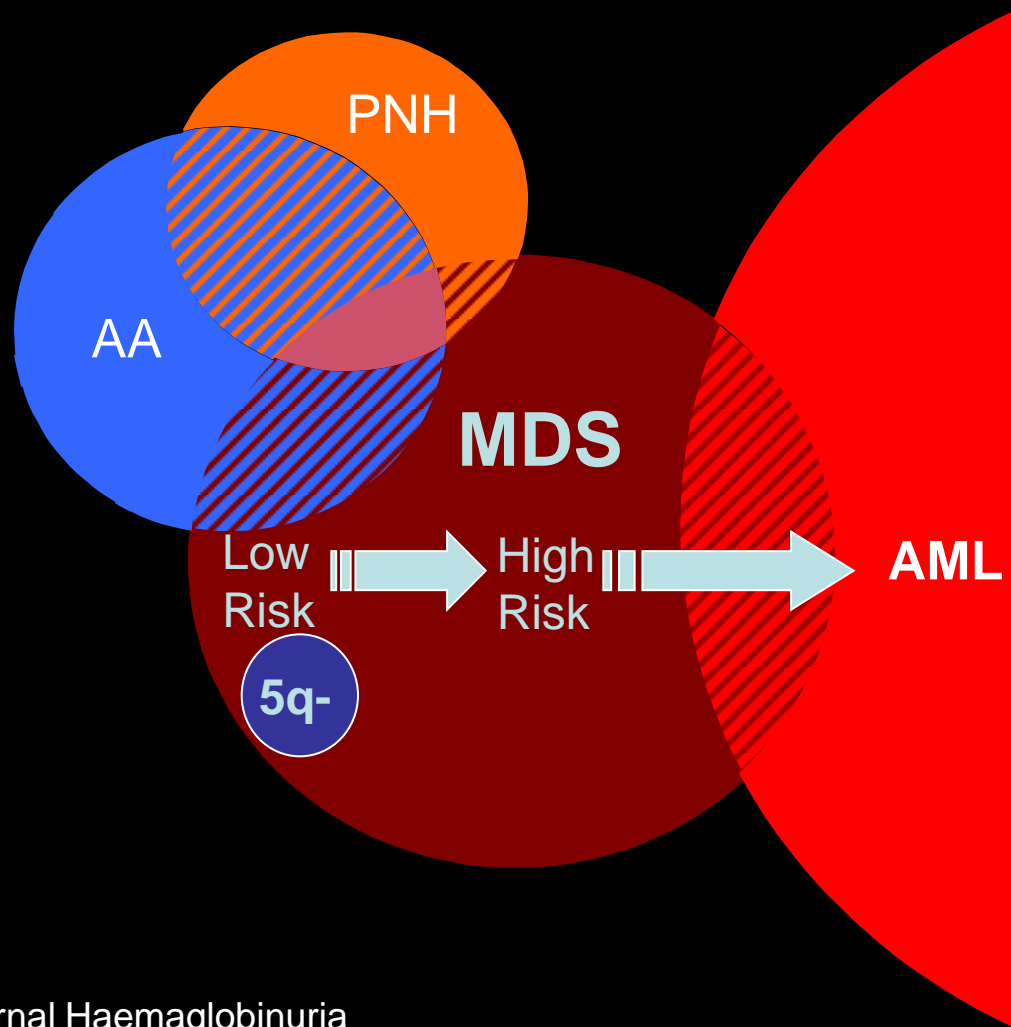
**Eurostat 2004-Percentage of people over
age of 60 years in 2031**

Hematologic Malignancy



MDS is in here – in the "shadowlands" between cancer and not cancer

The Bone Marrow Failure Syndromes



AA – Aplastic Anaemia

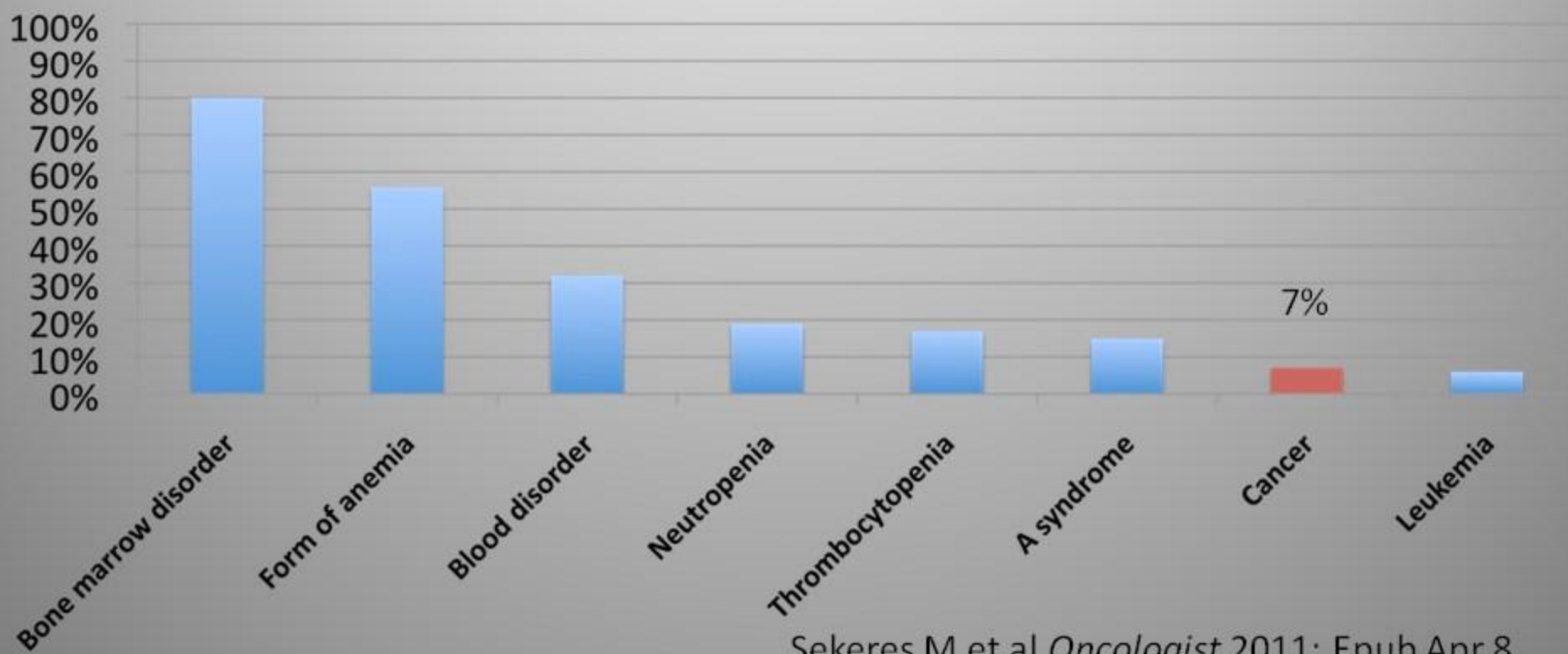
PNH – Paroxysmal Nocturnal Haemoglobinuria

Adapted from N. Young

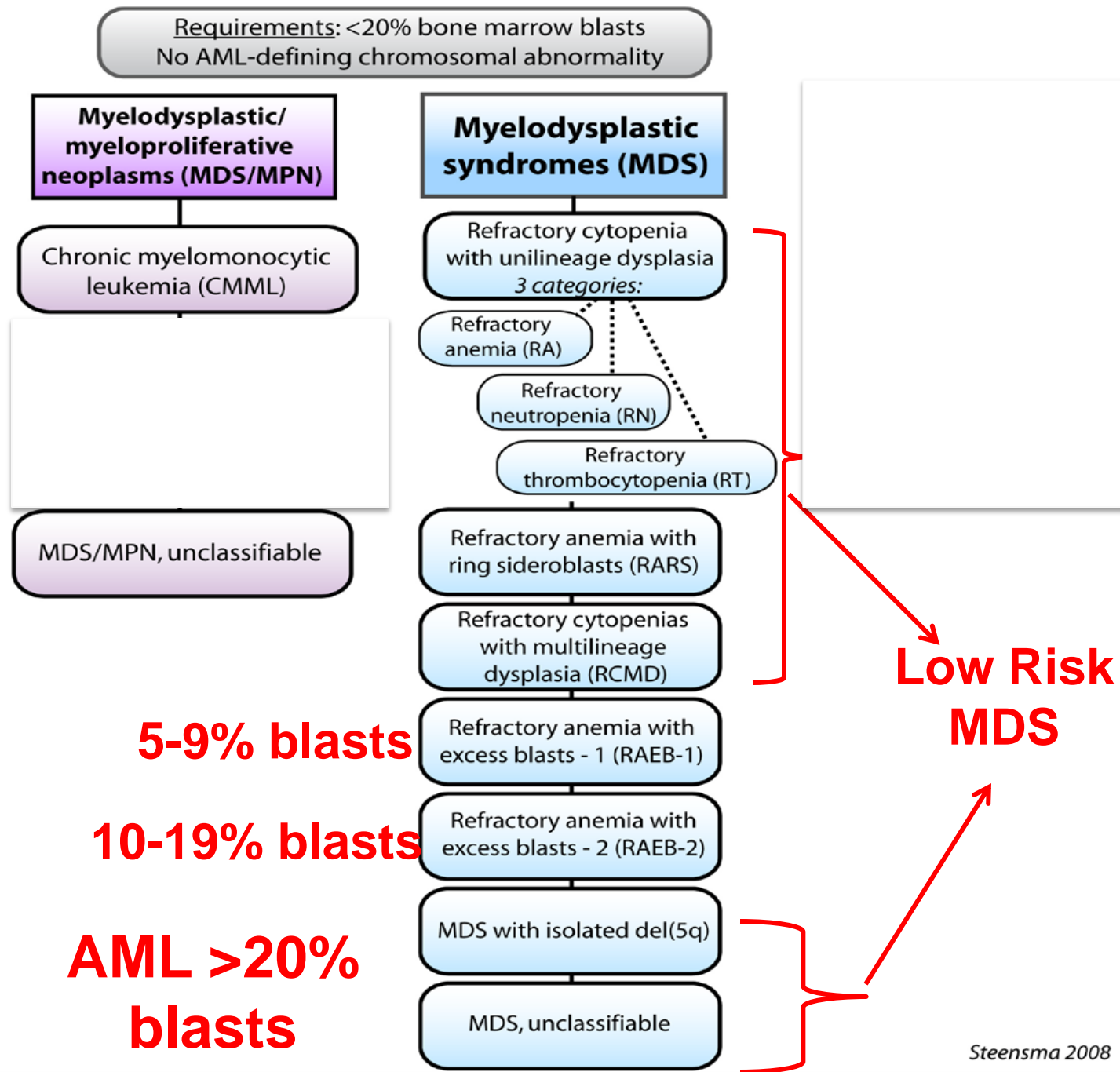
What do patients recall being told about MDS?



- Survey of 358 patients via AA&MDSIF:
 - How was MDS first described to you?*



2008 World Health Organization (WHO) Classification of Chronic Myeloid Neoplasms



MDS Classification – The *Ultimate* Simplification

- **Lower Risk** (Survival 3-10 years, low rate of AML)
 - RA, RARS
 - RCUD, RCMD
 - MDS-U, MDS del (5q)
 - IPSS Low, Int-1 (Score 0-1.0)
- **Higher Risk** (Survival <1.5 years, high rate of AML)
 - RAEB (-1, -2)
 - IPSS Int-2, High (Score ≥ 1.5)

International Prognostic Scoring System version 1.0 (1997)

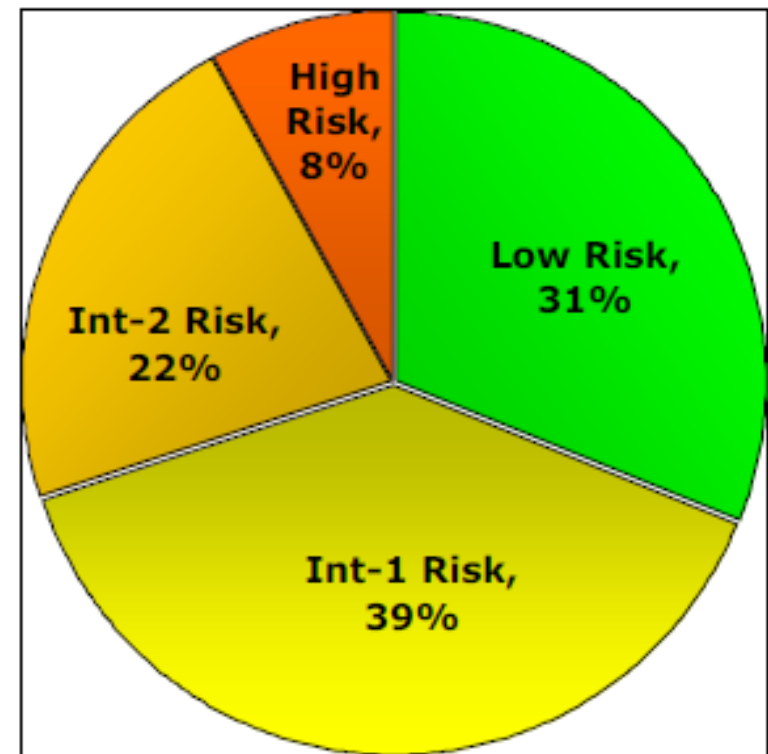
Prognostic Variable	Score				
	0	0.5	1.0	1.5	2.0
Marrow blasts (%)	<5%	5-10%	--	11-20%	21-30%
Karyotype class*	Good	Intermediate	Poor	--	--
# of cytopenias**	0 or 1	2 or 3	--	--	--

***Karyotypes:** Good = normal, -Y, del(5q) alone, del(20q) alone; Poor = chromosome 7 abnormalities or complex; Intermediate = other karyotypes

** **Cytopenias:** Hb < 10 g/dL, ANC <1800/uL, platelets <100,000/uL

IPSS Risk Categories: Patient Distribution And Outcomes

Score sum	IPSS Risk Category	Median survival for over age 60 group (years)	Time until 25% get AML (years)
0	Low	5.7	9.4
0.5-1.0	Int-1	3.5	3.3
1.5-2.0	Int-2	1.2	1.1
≥ 2.5	High	0.4	0.2



Patient Distribution

Therapeutic Options

- Low Risk MDS –
 - Main problem is anaemia, bleeding and recurrent infections
- High Risk MDS –
 - Main problem is bone marrow failure and risk of leukaemia

Treatment : general concepts

Treatment choices should take into account:

What type of MDS does the patient have?

Are any symptoms particularly bothersome?

Is curative therapy appropriate?

How aggressive is their MDS?

How does the patient want to be treated?

What age?
What other problems?

This is a Hard Truth

The only therapy capable of curing MDS is a bone marrow transplantation.

All other therapies improve blood counts, minimize transfusions, or improve quality of life.

If your blood counts and quality of life are fine, and you don't need transfusions, you may not need therapy.

Medications Currently Commonly Used for Patients with MDS

FDA Approved for MDS-Related Indications

Hypomethylating agents / DNA methyltransferase inhibitors / epigenetic drugs



Azacitidine (Vidaza ®)
Approved May 2004



Decitabine (Dacogen ®)
Approved May 2006

Immunomodulatory drug (iMiD)



Lenalidomide (Revlimid ®)
Approved December 2005

Iron chelators



Deferasirox (Exjade ®)
Approved November 2005

Deferoxamine (Desferal ®)
Approved 1968



FDA Approved for Other Indications

Blood cell (hematopoietic) growth factors

Red cell growth factors

Epoetin alfa (Procrit ®)

Darbepoetin alfa (Aranesp ®)

White cell growth factors

Filgrastim, G-CSF (Neupogen ®)

Pegfilgrastim (Neulasta ®)

Platelet growth factors

Romiplostim (NPlate ®)

Eltrombopag (Promacta ®)

Immunosuppressive drugs

Thalidomide, androgens, other biologics

Chemotherapy or stem cell transplant

Supportive care

Red cell transfusion	Anaemia causing symptoms
Platelet transfusion	Low platelets-bleeding & bruising Planned surgical operation
Erythropoietin	Anaemia
Granulocyte-colony stimulating factor	Infections associated with low white count
Antibiotic	Infections
Iron chelation therapy	Patients with low-risk disease with high transfusion requirement

Incidence of RBC Transfusion Dependence In MDS

IPSS Category	Proportion RBC Transfusion Dependent
Low Risk	39%
Intermediate-1 Risk	50%
Intermediate-2 Risk	63%
High Risk	79%

Red Cell Transfusion...The good



- Improves the oxygen carrying ability and improves symptoms
- Many patients will develop symptoms due to anaemia
- Red cell transfusion is the commonest way anaemia is treated
- The number and frequency may vary, but generally needs increase over time

- Sense of Altruism for donors-all voluntary

.....The bad



I might need a transfusion..



- Costly and decreasing donor pool
- Impacts on QOL, hospital attendances
- Transfusion reaction, infections and alloimmunisation
- Each unit has 250 mg of elemental iron

Chelation Clinical Guidelines

- Many organizations have guidelines for iron monitoring and iron chelation in MDS
 - At least 8 different guidelines in the last 10 years
 - Only partially evidence-based
- In general, these guidelines suggest:
 - **Periodic serum ferritin monitoring**, supplemented by other techniques for assessing iron burden
 - Consideration of iron chelation when patient has **persistent ferritin >1000 ng/mL** or other evidence of iron overload such as MRI, and lower-risk MDS
 - Start thinking about iron overload after **20-50 units RBCs**

Platelet transfusion-Liquid Gold



- Platelet transfusion should be reserved for patients with bruising or bleeding symptoms
- Planned surgery, dental extraction may also need to be covered by platelet transfusion

Therapy in low risk MDS

- Squeeze every ounce of production out of the remaining functional bone marrow cells by ERYTHROPOIETIN(EPO) and GROWTH FACTORS(eg GCSF)injections

ESAs/GF in MDS: Who Responds?



Treatment response score

s-epo	<100	+2
U/L	100–500	+1
	>500	–3
Transf	<2 units/m	+2
U RBC/m	= or >2 units/m	–2

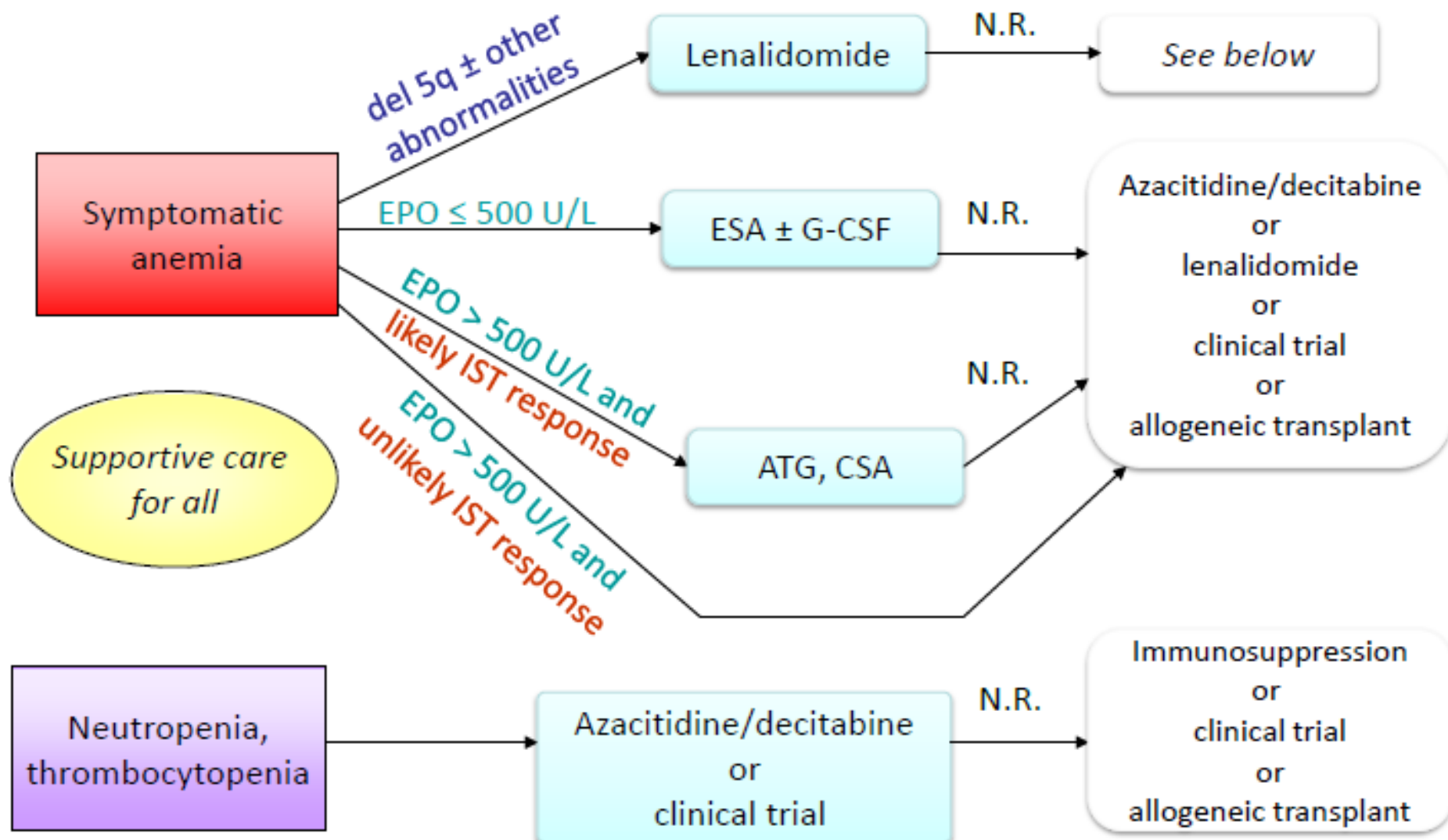
Therapy in low risk MDS

- Blocks the effects of nasty cytokines
(chemicals produced in excess by
abnormal bone marrow cells which can kill
the normal cells)

eg. Lenalidomide

ATG(horse or rabbit)

NCCN guidelines: lower-risk MDS (IPSS Low/Intermediate-1 Risk Groups)



High risk MDS

- Replace the bone marrow (and immune system)

Bone marrow transplant

Chemotherapy

Azacitidine/Decitabine

Clinical trials/ novel agents

Goal of Therapy: Higher-risk MDS

Prevent methyl groups from inactivating tumor suppressor genes and be directly cytotoxic – kill those bad cells!

- **Azacitidine (Vidaza)**
- **Decitabine (Dacogen)**

Azacitidine in high-risk MDS

It has been suggested that azacitidine may switch on important anti-cancer genes

Benefits include:

- Reduced red cell transfusion

- Improvement in survival

- Less chance of MDS deteriorating

- Results not influenced by patient age, blast cells, karyotype

Administered as injection into skin (oral azacitidine!)

For high risk patients ineligible for transplantation

Overall Survival: Azacitidine vs CCR ITT Population



Myelodysplasia

Intensive treatment

Bone marrow transplant should be considered when 'curative' therapy is thought to be appropriate.

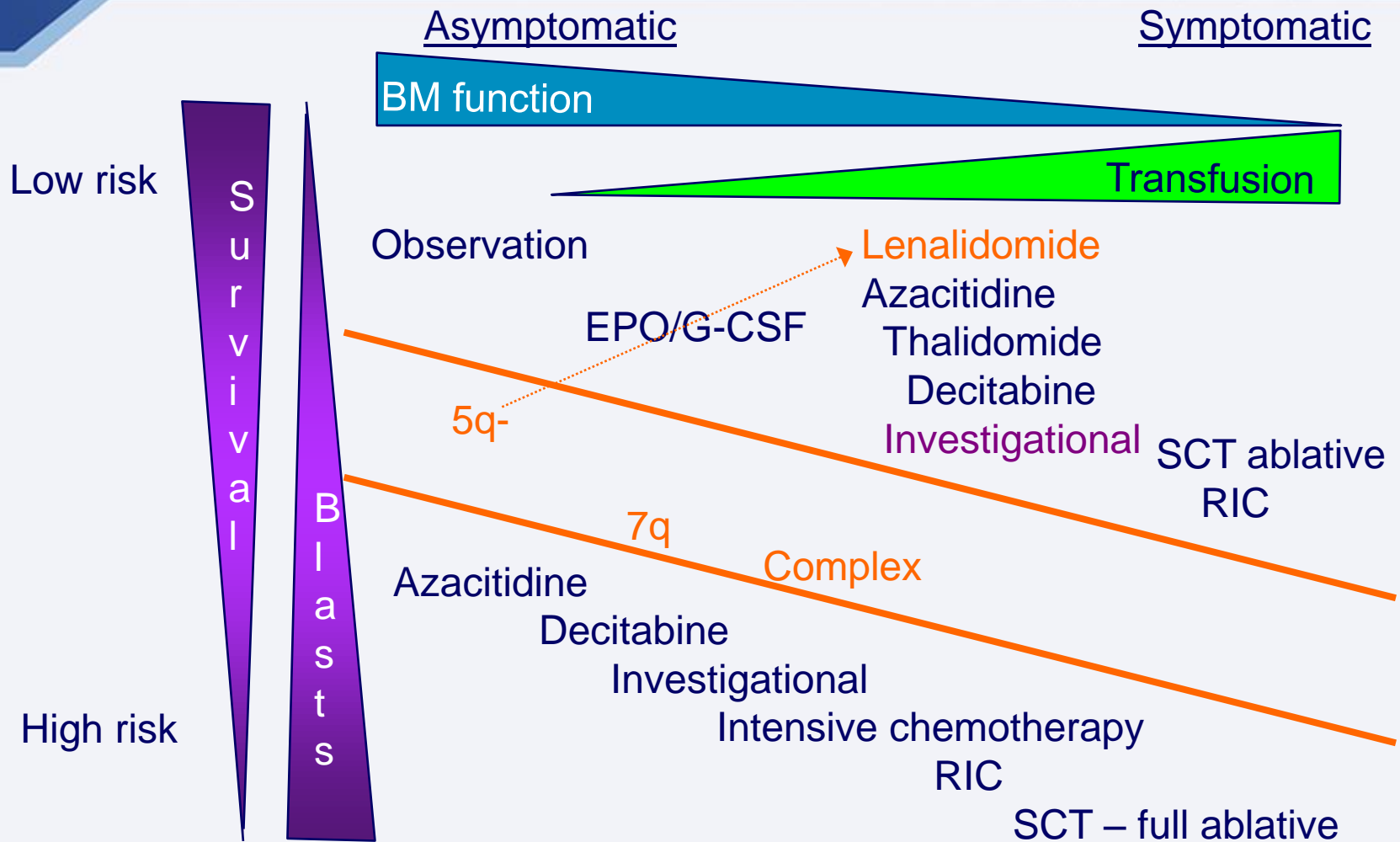
Key issues for patients:

Motivated, and deemed fit for BMT

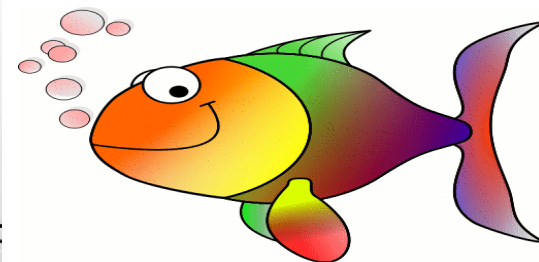
'High-risk' MDS, with disease under control

Appropriate counselling regarding outcomes, risks, and intensive long- term follow-up

Treatment algorithm for patients with MDS*



What do patients recall being told about MDS?



- Survey of 358 patients via AA&MDSIF

Table 1. Baseline demographics and disease characteristics

Characteristic	n = 358
Median (range) age, yrs	65 (19–91)
Male, %	49
Median (range) time since diagnosis, yrs	3 (0–29)
Median (range) time since first detection of abnormal blood profile, yrs	6 (0–59)
IPSS risk category, ^a %	
Low	28
Int-1	39
Int-2	23
High	9
Bone marrow not known, %	42
Cytogenetic status not known, %	28
Cytopenias, %	
Anemia	82
Thrombocytopenia	46
Neutropenia	45
Blood transfusions, %	65
Within 3 mos	52
Treatments in the last 3 mos before survey, %	
Darbepoetin	55
Epoetin	49
Active therapies	
Azacitidine	51
Lenalidomide	39
Decitabine	56
Antithymocyte globulin	11
Stem cell or bone marrow transplantation	10
Enrollment in a clinical trial	24

^aOnly 45% of all patients knew their IPSS score.
Abbreviations: Int, Intermediate; IPSS, International Prognostic Scoring System.

Abnormal
blood test

3
Y
E
A
R
S

Diagnosis of
MDS

Table 2. Patient-reported number of days when health was “not good” or restricted activities in the last 30 days

Parameter	Overall	By treatment ^a		By IPSS risk group		<i>p</i> -value
		Active treatment	Supportive care	Lower risk	Higher risk	
Not good physical health, days	8.3	8.8	8.1	5.7	8.1	.02
Not good mental health, days	6.8	7.0	6.7	4.1	8.2	.01
Physical or mental health restricting usual activities, days	6.8	7.9	6.4	4.1	9.3	< .001

^aThere were no significant differences between active treatment and supportive care for each parameter investigated. Abbreviation: IPSS, International Prognostic Scoring System.

Conclusions

- MDS is more common than you think!
- Most people with MDS have some anemia
- We can delay therapy until symptoms or transfusions demand it
- Therapy choices depend on whether you have lower- or higher-risk MDS – so make sure you ask your doctor your MDS subtype & IPSS Score!

100

QUESTIONS & ANSWERS

What is
myelodysplastic
syndromes
(MDS)?

Is MDS a cancer?

How is MDS
diagnosed?

How do I know
which treatment is
best for me?

About
**Myelodysplastic
Syndromes**



by
Jason Gotlib, MD, MS
Lenn Fechter, RN, BSN



 **MDS**
UK Patient
Support Group

Prof Ghulam Mufti

**Staff and patients at
Kings College Hospital**

**LEUKAEMIA
& LYMPHOMA
RESEARCH** 

Beating Blood Cancers