Update on Treatments for Myelodysplastic Syndromes

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Off Label Uses: Erythropoietin, Darbopoietin, G-CSF for treatment of MDS

Review MDS and Potential Treatments

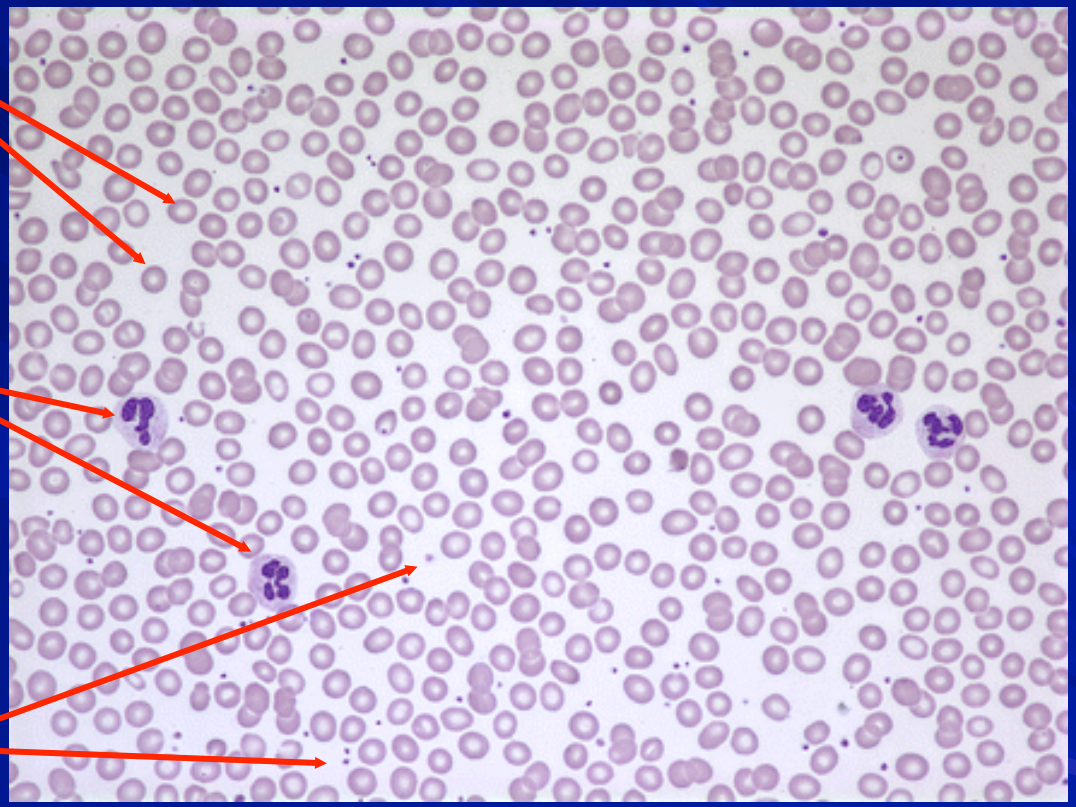
- What is MDS
- How can we assess MDS
- What can we do for patients with MDS

Your Blood – What's in It?

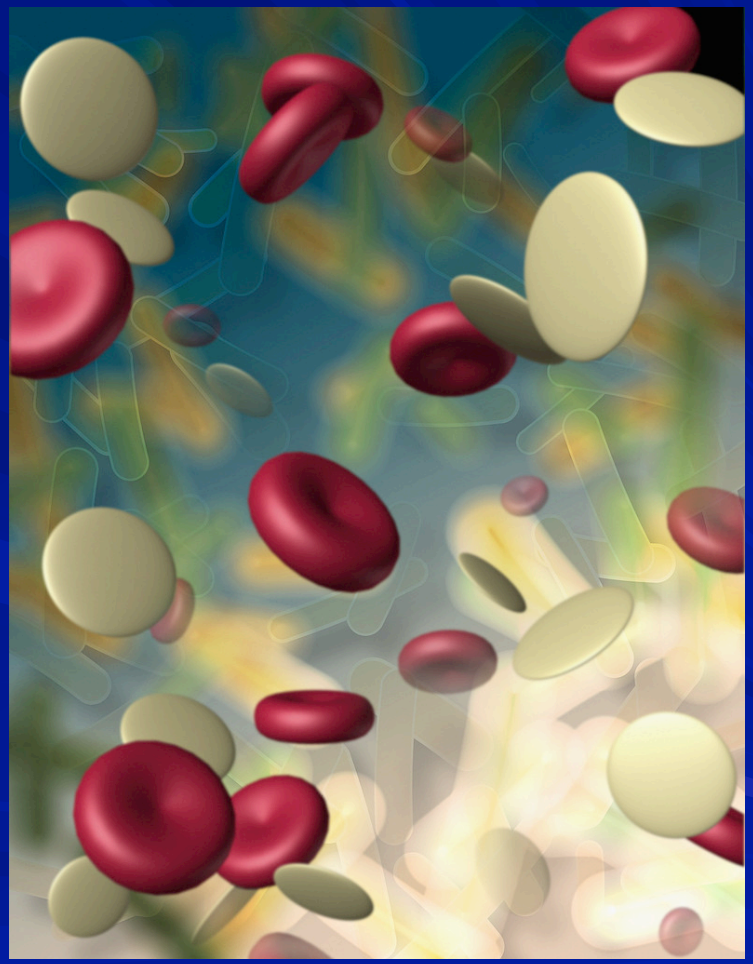
Red Blood Cells:
- Carry oxygen throughout the body

White Blood Cells:
- Fight infections

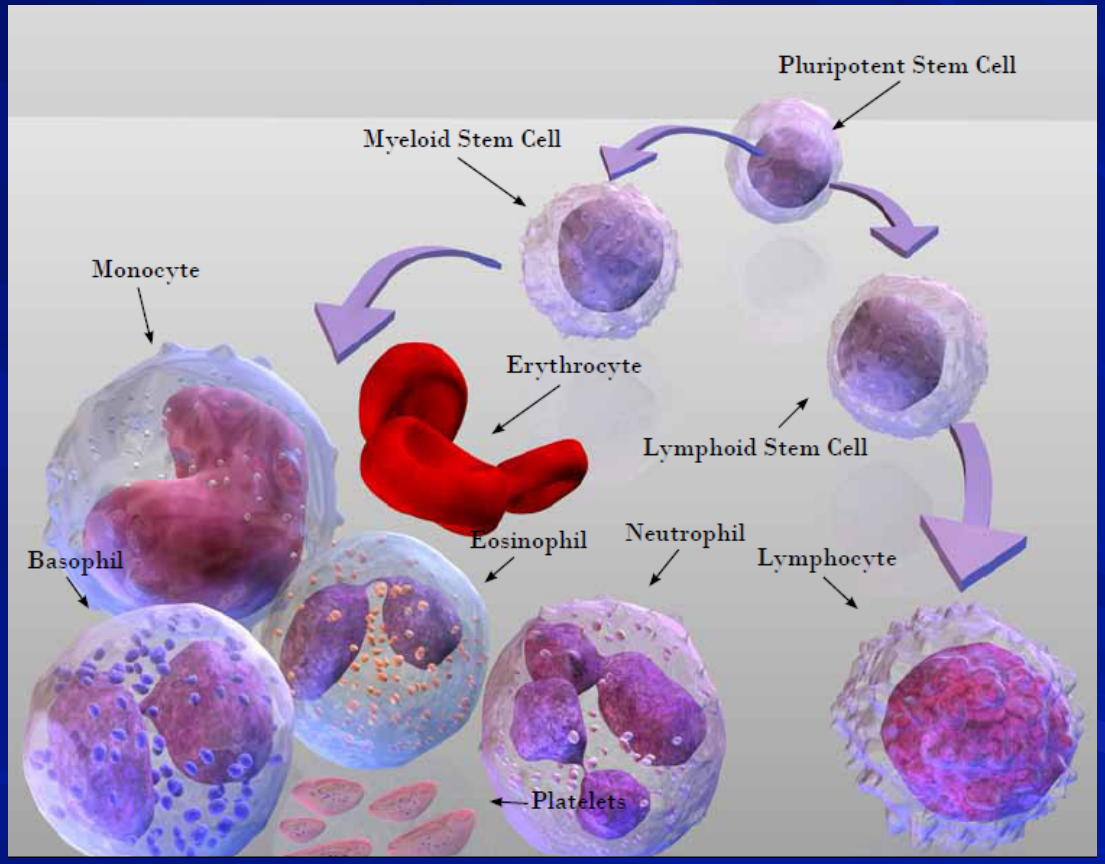
Platelets:
- Tiny cells that aid in blood clotting



Blood Cells are Generated in the Bone Marrow to Replace Cells that Die Off



Blood Cells all Come from a Stem Cell

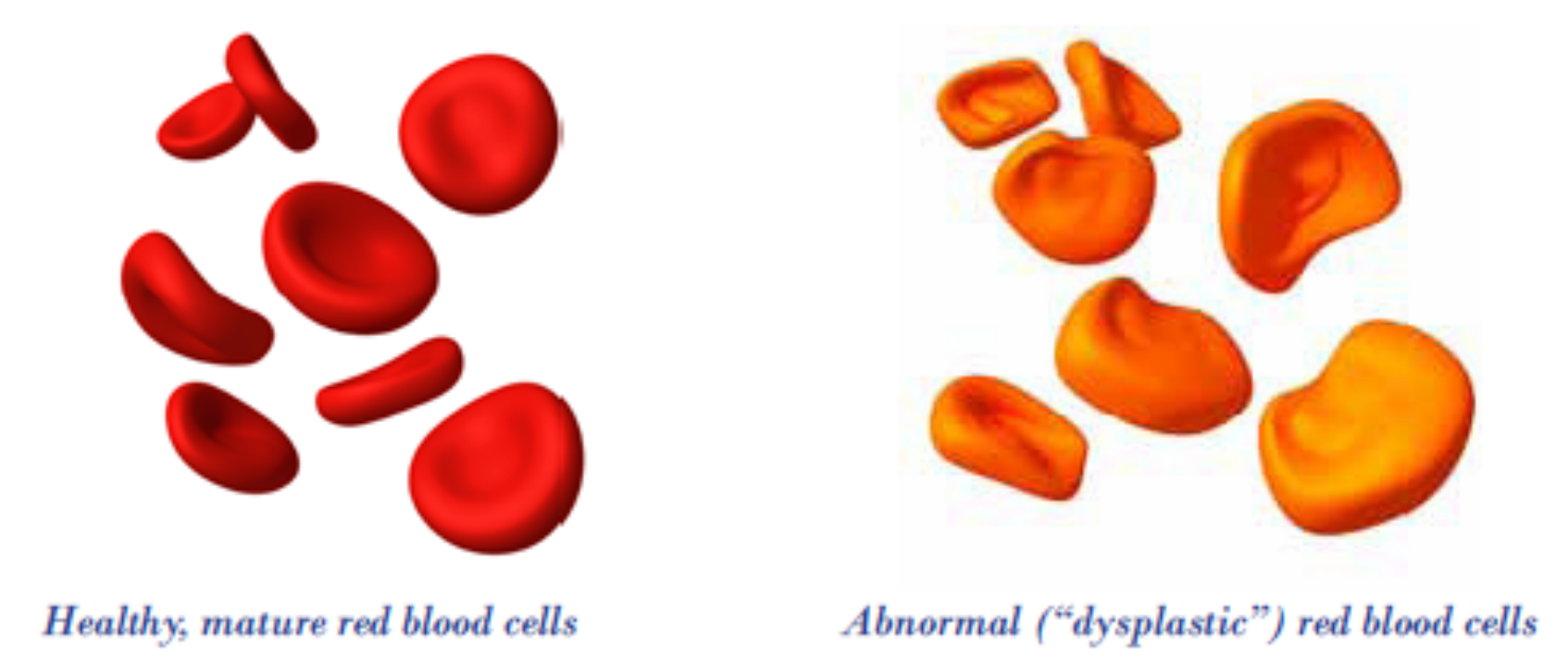


http://www.mds-foundation.org/wp-content/uploads/2011/10/BoneMarrowBook.pdf

What is Myelodysplastic Syndrome?

- MDS is a disease of the stem cell of the marrow.
- It is a form of cancer
- Stem cells grow, divide but do not develop normally into mature cells
- Unhealthy and disordered cells build up in the marrow
- Most cells die before they can be released

What is Myelodysplastic Syndrome?



Healthy, mature red blood cells

Abnormal ("dysplastic") red blood cells

http://www.mds-foundation.org/wp-content/uploads/2011/10/BoneMarrowBook.pdf

What Happens if Bone Marrow Stops Working?

- Low Red Blood Cell Counts – “Anemia”
  - Less energy, shortness of breath
- Low White Blood Cell Counts – “Leukopenia”
  - Increased risk of infection
  - Often focuses on a specific white blood cell: the neutrophil
- Low Platelet Counts – “thrombocytopenia”
  - Increased risk of bleeding
  - Severity of risk depends on how low the platelets are

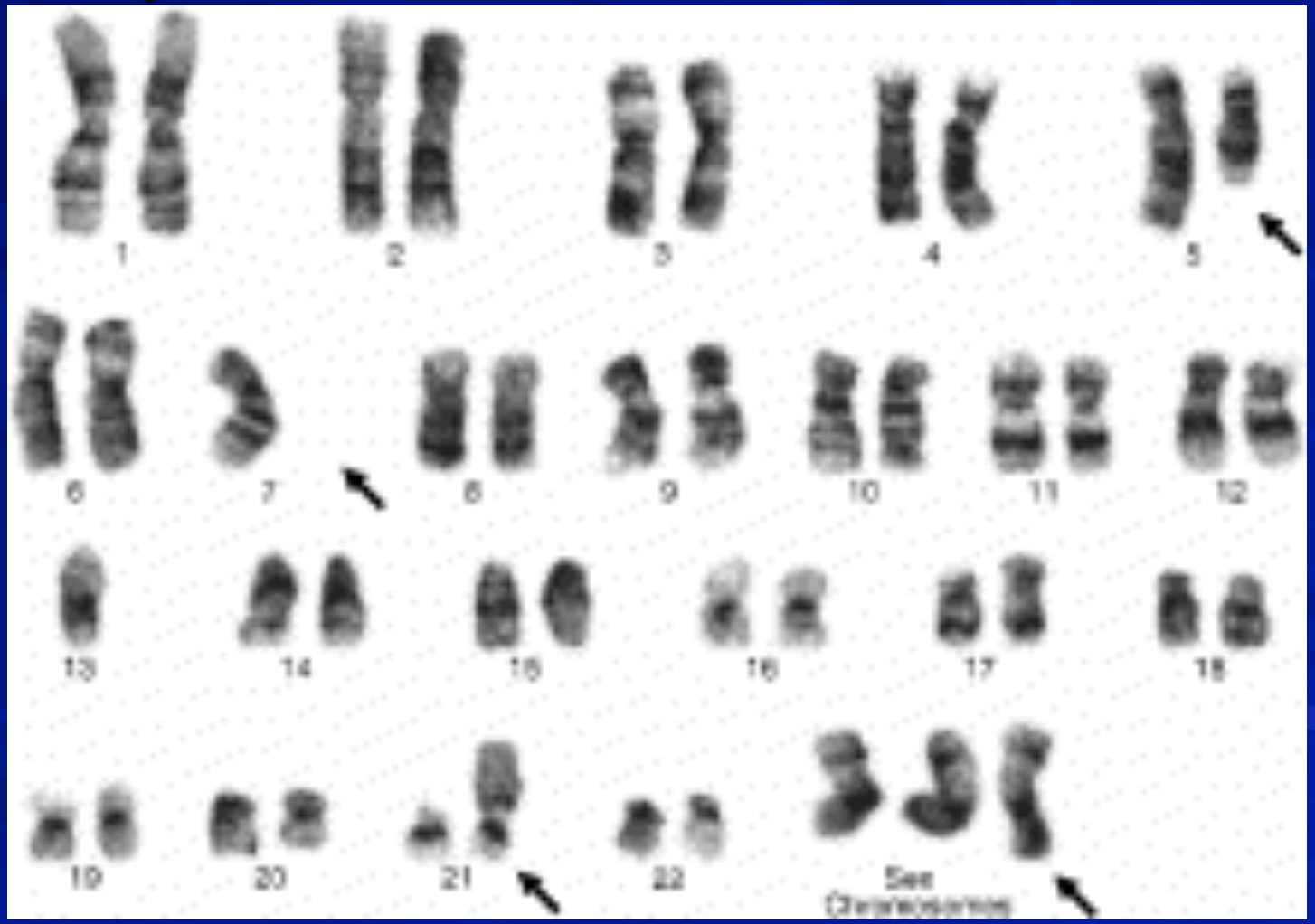
Myelodysplastic Syndromes

- A spectrum of diseases where the bone marrow cells are damaged and cannot mature properly
- Low blood counts are the norm
- Sometimes damage is seen in the chromosomes of the bone marrow
- Some cases (30%) will go on to develop acute leukemia (AML) over time

Causes of MDS

- 75% of patients are older than 60
- Some patients have been exposed to toxins or drugs
  - Benzene and solvents
  - Chemotherapy
  - Radiation
- Occasionally a patient with aplastic anemia will go on to develop MDS
- Most cases the cause is unknown

Chromosome Dammage is important in MDS assessment



Olney, HJ and Le Beau, MM (2006), Leukiemia Research

What happens in MDS?

- Patients eventually get sicker from low blood counts
- Many, but not all patients, will see deterioration in the bone marrow
  - More genetic changes over time
  - Accumulation of cells with no maturity whatsoever – blast cells
- When the blast cell number exceeds 20% we say transformation to acute leukemia has occurred
  - Usually a catastrophe

Treatments for MDS

- Depend on how severe the MDS is
- “Risk Score” is assigned based on
  - Number of cell types affected
  - Presence and type of chromosome damage
  - Number of immature cells called blasts in the marrow
  - (need for transfusions)
- Patients can be divided into low and high risk groups

Risk Groups of MDS

- Lower risk patients – about 2/3
  - Fewer symptoms
  - Less likely to become AML
  - Live longer
- Higher risk patients – about 1/3
  - More symptoms, need more support with transfusions
  - Increased risk of becoming AML
  - Shorter life expectancy

Treatments for MDS

- Supportive transfusions
  - Iron Chelation
- Growth Factors – ESAs + GCSF
- Immunosuppressive therapy
- Hypomethylating agents
- Intensive Chemotherapy
- Allogeneic Stem Cell Transplantation

Therapies generally considered for lower risk MDS

Therapies generally considered for higher risk MDS

- Important to choose the appropriate therapy
  - Disease –related factors
  - Patient related factors

Treatment of Lower Risk MDS

- Goals of Treatment:
  - Reduce transfusion needs
  - Improve quality of life
- Treatments should
  - Be easy to take
  - Few side effects
- Some patients with lower risk MDS may not need any treatment at all

Supportive Care

- Helpful in all cases of marrow failure
- Transfusions
  - Red Blood Cells
  - Platelets
  - White blood cells not routinely transfused
- Antibiotics

Transfusions

- Nearly all patients will need a transfusion at some point in their journey.
  - Red blood cells
  - Platelets
- No magic numbers!
- Generally safe with fewer than 1/1000 transfusions resulting in a significant reaction

Iron Overload

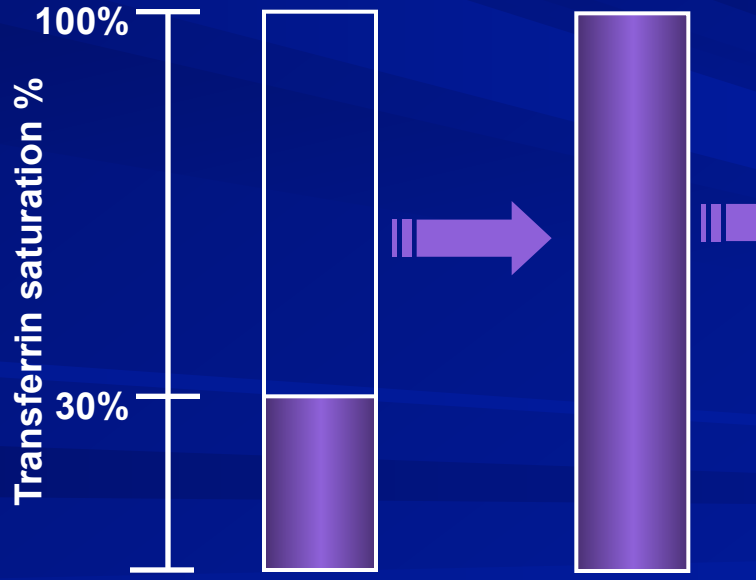
- Each unit of red cells transfused
  =
  200 – 250 mg Fe
- > 100 x usual intake.
- GI absorption of Fe is enhanced in MDS patients.
- Increased prevalence of hereditary hemochromatosis in MDS patients.

Iron loading in transfusion-dependent patients

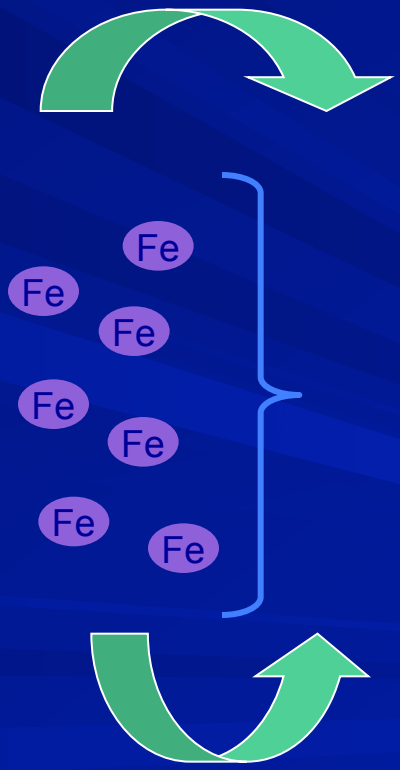
Iron overload due to
- Frequent blood transfusions and increased iron absorption

Normal: body can manage iron levels

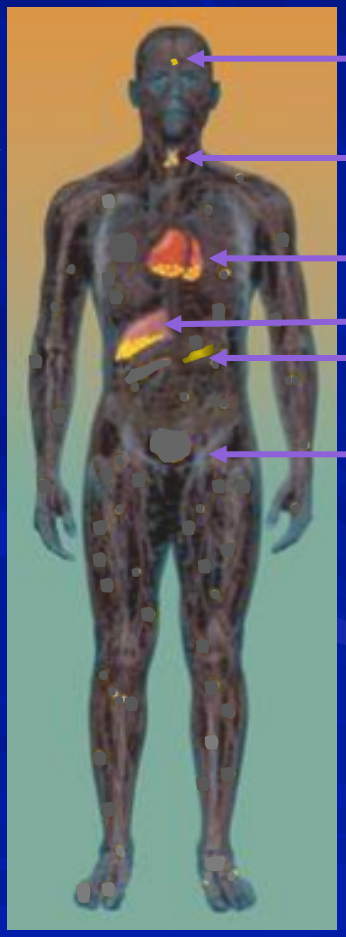
Iron overload



Subsequent formation of reactive iron in blood



Uncontrolled iron loading of organs



Iron Chelation

- The body cannot remove excess iron on its own
- Chelators are drugs that allow removal of body iron

- Two drugs licensed in Canada
  - desferoxamine (Desferal) given as an infusion overnight
  - deferasirox (Exjade) given orally – newer drug, easier to take

- Have been shown to help reduce iron damage in patients who receive blood over long periods of time

Immunosuppressive Therapy (IST)

- Based on the observation that immune cells appear to play a role in development of MDS
- Many different regimens exist to suppress the immune system
- Seems to work in certain patients, but not others
  - Certain types of low risk MDS
  - Certain genetic backgrounds
  - Younger patients

Immune therapy in MDS

- Some lower-risk MDS patients may also respond to ATG and cyclosporin
  - Less than 60 years old
  - Low cell counts in marrow
  - Sick for less than 1 year
- May be component of immune effects in MDS as well as aplastic anemia

Effectiveness

- IST can improve cell counts in about 30% of selected patients
- Time to response is slow, can take weeks or even months until blood counts improve
- Some patients require long-term treatment to maintain blood counts
- Risks of infections while on treatment

Treatment with Red Blood Cell Growth Factors

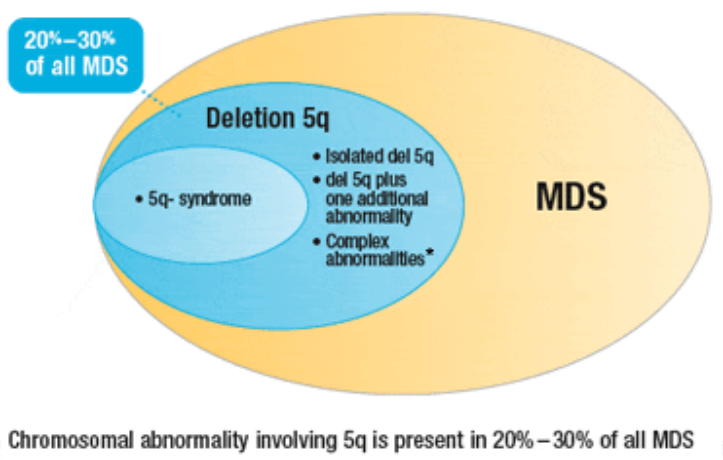
- Erythropoietin (Eprex) and darbopoietin (Aranesp)
- Synthetic hormones that stimulate marrow to make red blood cells
- Usually given as a needle under the skin
- Can increase red blood cells, but not white cells or platelets
- Sometimes given with another factor called G-CSF

Other growth factors

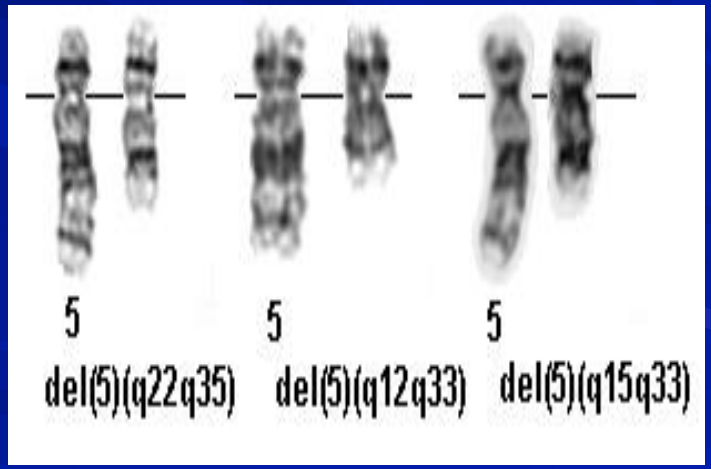
- Platelet stimulating drugs
  - Have not yet been proven safe for patients with MDS
  - May even make things worse!
- White blood cell stimulating drugs
  - Sometimes used, but on the whole do not appear to make much difference for patients

Lenalidomide

- Effective versus MDS with 5q minus
- A minority of patients with MDS (5-20%)
- 5q- Syndrome = anemia, increased platelets, low blast count.



Chromosomal abnormality involving 5q is present in 20%–30% of all MDS



Lenalidomide - effectiveness

- Oral medication, taken daily
- Approximately 2/3 of patients with del 5q MDS become transfusion independent.
- Most responses occur within 3 months
- Effects last for up to four years on average

Lenalidomide

- Toxicities
  - Low white blood cells and platelets may be seen, but are usually manageable
- MAJOR risk for birth defects
- ALL physicians and patients involved must be enrolled on RevAID programme
  - (lots of paperwork to track drug, ensure no foetal exposure occurs)

Lower risk MDS - Summary

- Patients will enjoy relatively long life
- Treatments should be easy to take and not interfere with daily life
- Some options include
  - Watch and wait
  - Transfusions with or without iron chelation
  - Erythropoietin
  - Lenalidomide if 5q minus
  - ATG and cyclosporin in some patients

Treatment of Higher Risk MDS

- Patients have signficiant risk of AML and death within a year of diagnosis
- Usually need more transfusions, have more frequent infections

- Goals of treatment
  - Prolong life
  - Reduce risk of transformation to AML
  - Reduce needs for transfusions and antibiotics
  - Accept more toxicty and interference with quality of life

Curing Higher Risk MDS

Bone marrow or Stem Cell Transplant

- Majority of patients are ineligible
- Risk of transplant increases with age
- Many will not have a well-matched donor
- Results are not perfect
  - Only about 40% of patients undergoing transplant are cured
  - About 30% of patients may die from complications of the transplant
  - About 30% will relapse their disease
  - Many major side effects
  - Timing of transplant critical (risk/benefit consideration)

Gore S. *Cancer Control* 2004; 11:3-6
Alberta Cancer Board, *Clinical Practice Guideline LYHE004*, Nov 2007

Stem cells can come from either blood or bone marrow

Azacitidine (Vidaza) for Higher-Risk MDS

- Old chemotherapy drug currently experiencing a renewal
- Shown to both slow the growth of defective cells and may help cells behave more normally
- New class of drugs called hypomethylating agents

Azacitidine for higher-risk MDS

- Large study on patients with higher-risk MDS showed that patients
  - Lived longer (about twice as long)
  - Less likely to need transfusions or antibiotics
  - Had an improved quality of life
  - Much less likely to die
- Azacitidine is given as a needle under the skin every day for a week each month
- Controls but does not cure MDS
  - Must be given each month without stopping

Azacitidine for higher-risk MDS

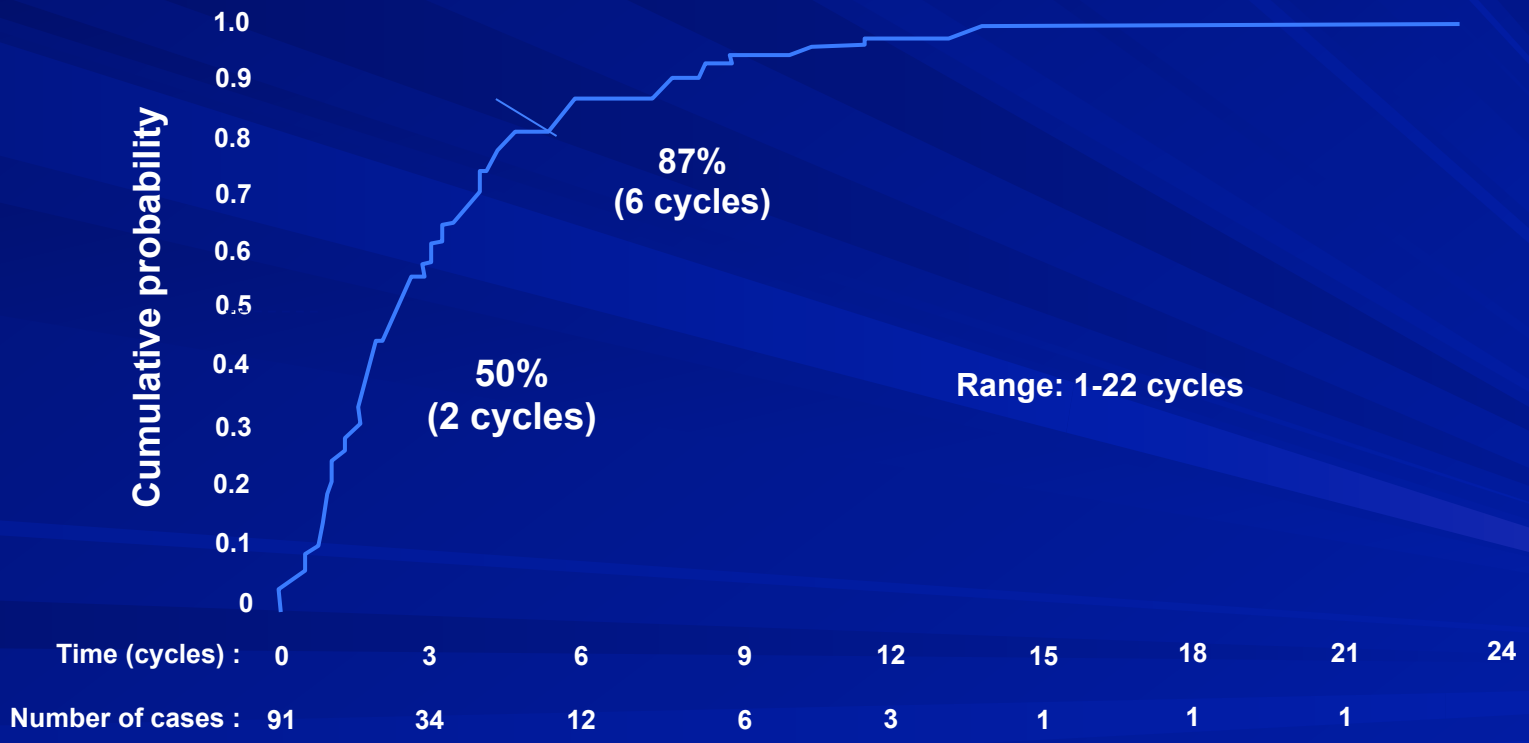
- About half of patients will become independent of transfusions
- Less chance of significant infection
- Slower evolution to AML
- Life expectancy improved – on average doubled for higher risk patients
  - This effect on improved lifespan is seen even if there is no other benefit observed – as long as there is no progression.

Azacitidine for higher-risk MDS

- Generally well tolerated
  - Local injections can be painful
  - Some nausea – also constiptation
  - Evening Primrose oil and flax seeds
- May make blood counts worse in first cycles
  - Increased risk of infections
- Slow to act

Prolonged Treatment With Azacitidine Improves Responses in MDS

- **Response after 2 to > 6 cycles**
- **Continuing treatment improves responses in 48% of cases**



Silverman LR et al, Blood (ASH)

Decitabine (Dacogen)

- Another hypomethylating drug that works similarly to azacitidine
- Still being studied but has not shown the same effects on longevity as azacitidine
- Approved in the USA but not in Canada

Higher Risk MDS Treatments: Summary

- Stem cell transplantation is a consideration for some
- For most patients treatment with 5-azacitidine is the best standard option available in 2013
- Participation in a clinical trial can also be considered

New Directions

- Little work in early detection or prevention
  - We have yet to understand why most people get MDS
- Many drug trials
  - New drugs (many)
  - Combination strategies
    - Lenalidomide+azacitidine among other combinations
  - New approaches to stem cell transplantation

Conclusions

- Increasing number of treaments for marrow failure syndromes
- Some cures
  - Aplastic Anemia
  - Transplantation
- Particular strides being made in treatment of MDS