Update on Drug Treatments for Marrow Failure Syndromes

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

Review New Therapies

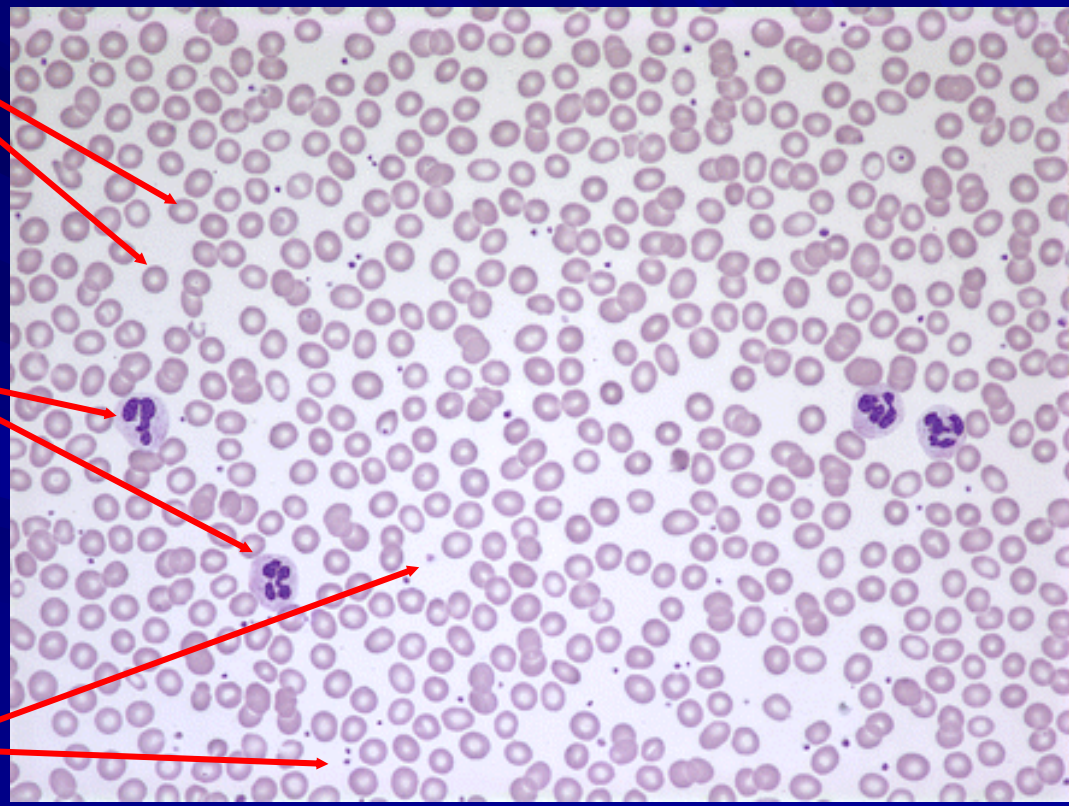
- Aplastic Anemia
- Myelodysplastic Syndromes
- Paroxysmal Nocturnal Hemoglobinuria (PNH)

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



Maslak, P. ASH Image Bank 2008;2008:8-00067
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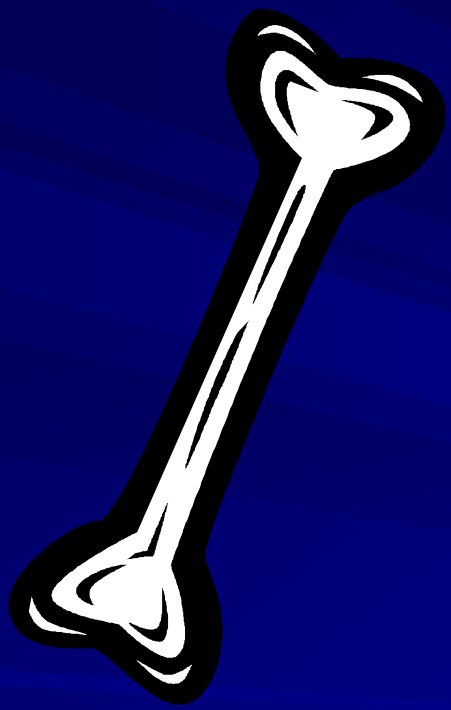
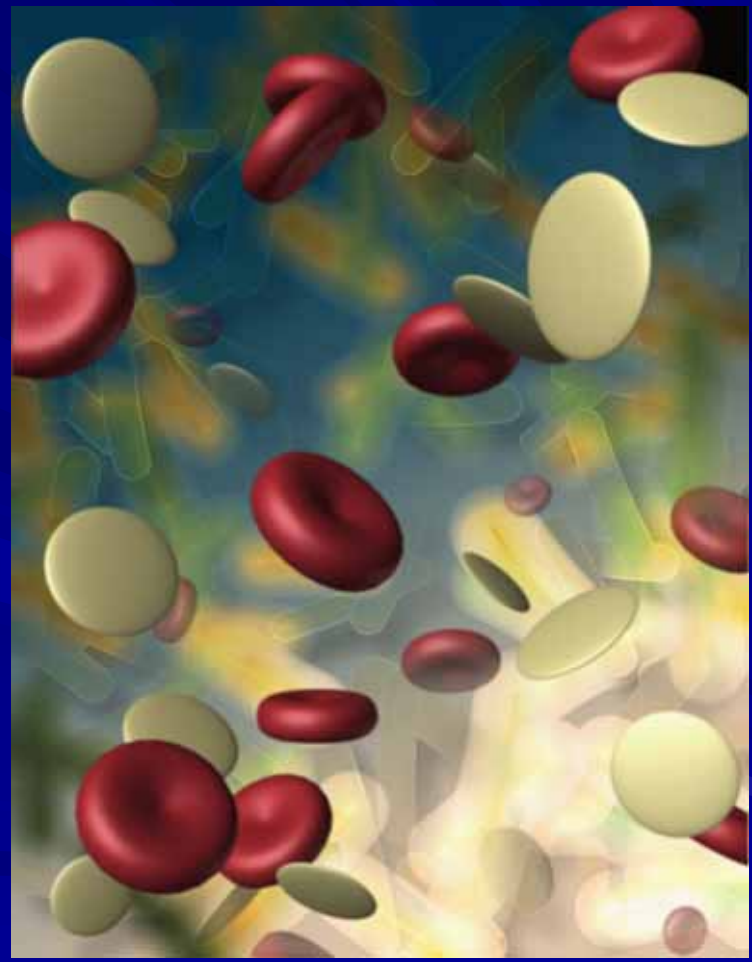
Blood Cells are Generated in the Bone Marrow to Replace Cells that Die Off





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

Supportive Care

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

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.

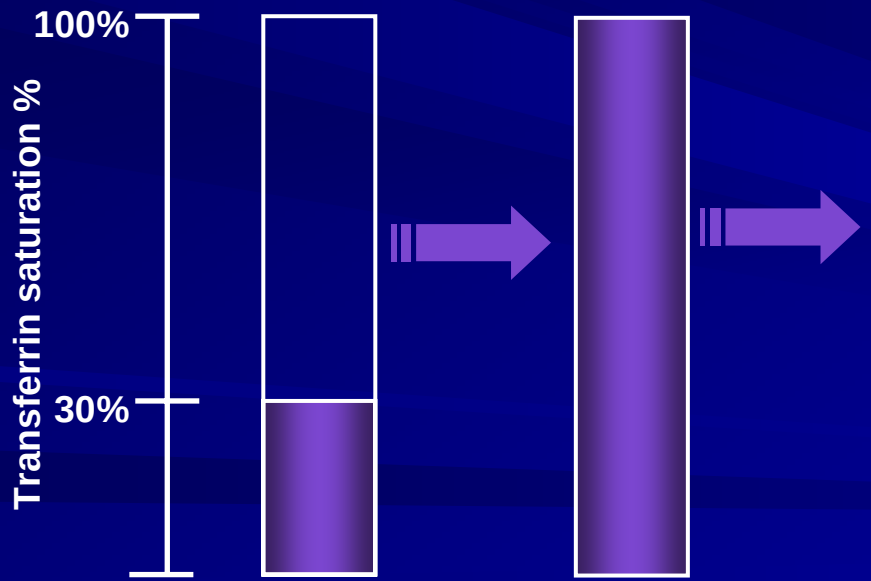
- Increased prevalence of hereditary hemochromatosis in MDS patients.

Iron loading in transfusion-dependent patients

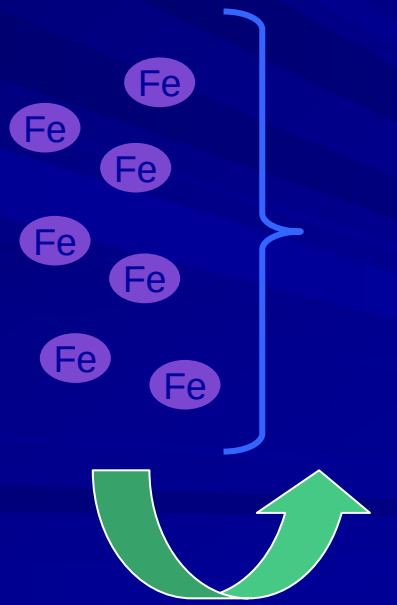
Iron overload due to
- **Frequent blood transfusions and increased iron absorption**

Normal: body can manage iron levels

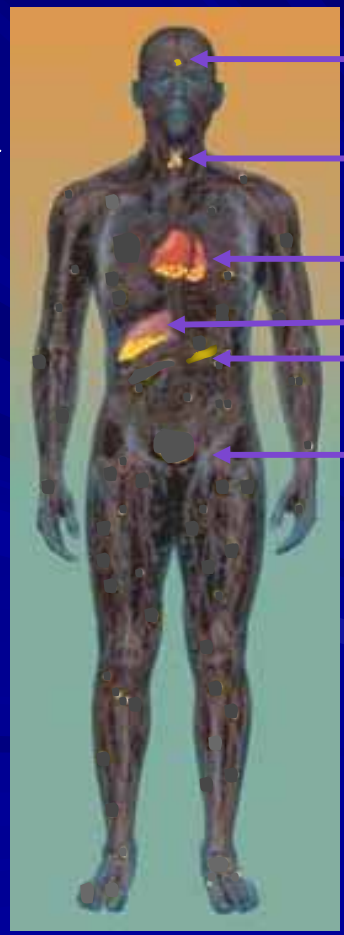
Iron overload



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

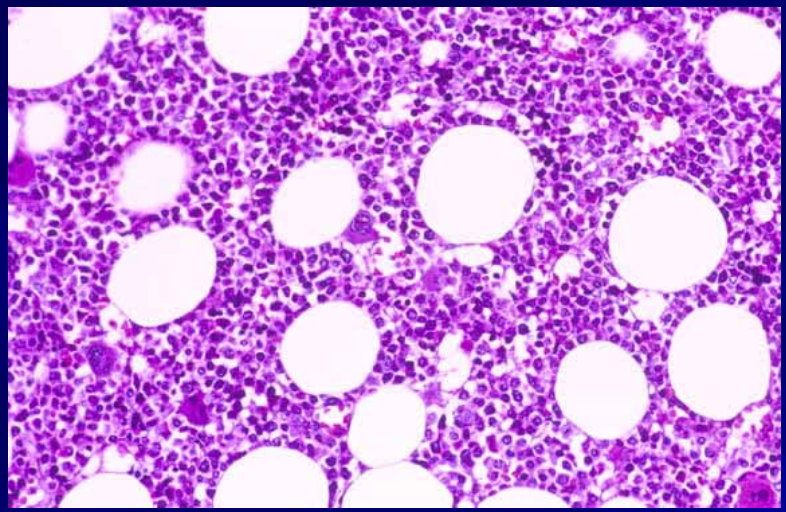
- Two drugs licensed in Canada
  - desferoxamine (Desferal) given as an infusion overnight
  - deferasirox (Exjade) given orally – newer drug

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

Aplastic Anemia

- Loss of Bone Marrow Cells
  - Replaced by fat
- Rare in North America (3-6 cases per million/year)
  - More common in Asia
- Causes
  - Drugs and toxins
  - Infections
  - Pregnancy
  - Inherited disorders (rare)
- The majority of cases are of unclear origin
  - Immune system is believed to be involved

Normal and Aplastic Marrow



- Normal Marrow
  - Full of cells of all types
- Aplastic Marrow
  - Mainly fat cells seen

Treatment of Aplastic Anemia

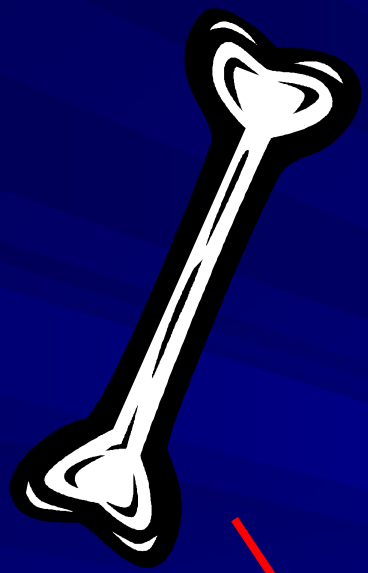
- Aplastic anemia may be:
  - Moderate – low blood counts but little symptoms
  - Severe – neutrophil count less than 500 (or 0.5)
  - Very severe – neutrophil count less than 200 (or 0.2)
- High risk of death from infection and bleeding if severe or very severe
- Rare cases may be reversed if offending drug or toxin can be removed
- Most patients will require some form of treatment

Stem Cell Transplantation

Replacing bone marrow cells with cells from healthy donor

- Requires a “matched” donor
  - Usually a brother or sister, can be unrelated
  - NOT “blood type” (A, B, O) but rather a very complex set of “tissue types” called HLA
- Involve using high doses of chemotherapy and radation to kill the remaining bone marrow and replacing it with those from the donor

Stem cells can come from either blood or bone marrow



Transplantation for Aplastic Anemia

- Risky with many side effects
  - From chemotherapy and radiation
  - From the new bone marrow
- Works best in patients under 40 years with a well-matched donor
  - Must be in otherwise good health

Immunosuppressive Therapy (IST) for Aplastic Anemia

- Based on the observation that immune cells appear to play a role in development of AA
  - T-lymphocytes appear to be critical
  - Immune driven attach on the marrow
- Many different regimens exist to suppress the immune system
- Often combinations of different drugs are used
  - ATG (also called anti-thymocyte globulin or ATGAM)
  - Cyclosporine
  - Prednisone

ATGAM – Anti-Thymocyte Globulin

- Biological product made from horse serum
- Antibodies to human T-lymphocytes
- Tricks the body into destroying these cells
- Usually given in hospital over several days
- May cause severe reactions including
  - Rashes
  - Chills and shakes
  - Anaphylaxis (shock)

Other Drugs

- Cyclosporine
  - Oral medicine that suppresses immune cell function
  - Can cause high-blood pressure and kidney damage
  - Rare cases of brain swelling
  - Levels of drug must be carefully checked
- Prednisone
  - Another immune suppressing drug
  - Also helpful controlling reactions to ATGAM
- Often ATGAM, cyclosporine and prednisone are used together to treat AA - most effective treatment

Effectiveness

- IST can improve cell counts in many cases of AA
  - About 70% overall with moderate and severe cases responding better than very severe
- 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

Newer Treatments for Aplastic Anemia

- Alemtuzumab (Campath ®)
  - Engineered antibody to lymphocytes
    - Fewer reactions
    - May be more potent
  - In trials to see if it is better than ATGAM in controlling responses
- Cyclophosphamide
  - Older chemotherapy drug that may be able to create responses in AA
- Clinical trials are ongoing in North America for these and other drugs

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

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
  - Fewer symptoms
  - Less likely to become AML
  - Live longer
- Higher risk patients
  - More symptoms, need more support with transfusions
  - Increased risk of becoming AML
  - Shorter life expectancy

Treatment of Lower Risk MDS

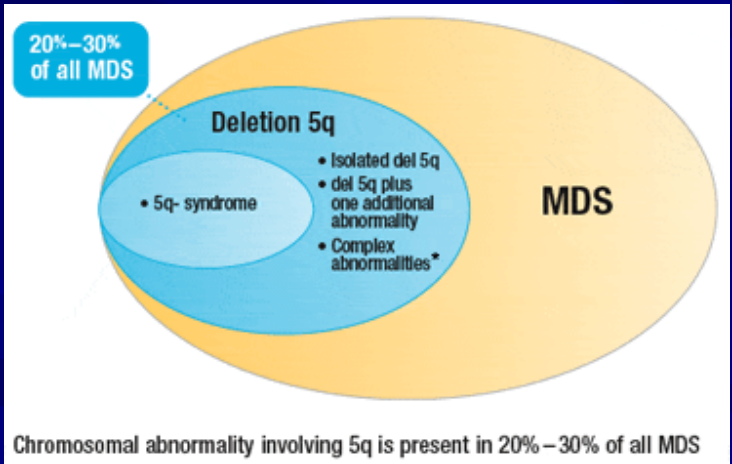
- Goals of Treatment:
  - Reduce transfusion needs
  - Improve quality of life
- Treatments should
  - Be easy to take
  - Few side effects
- Some patients with lower risk MDS may not need any treatment at all

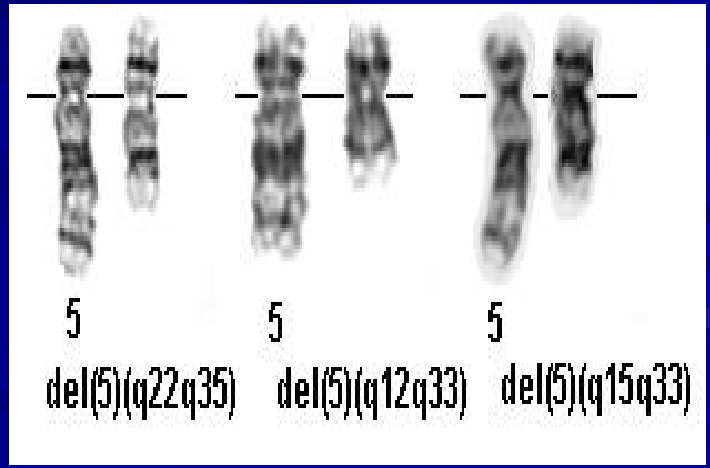
Treatment with Red Blood Cell Growth Factors

- 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

Lenalidomide

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





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)

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

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

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
  - 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

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

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

PNH: Paroxysmal Nocturnal Hemoglobinuria

- VERY rare condition
- Marrow can no longer make certain proteins on the surface of blood cells
  - Proteins protect the cells from the immune system (complement, a cell destroying group of proteins)
- Cells are attacked by immune system and are destroyed

Effects of PNH on the body

- Patients experience loss of hemoglobin (the protein of red blood cells) in the urine
- Anemia quickly develops and patients need frequent transfusions
- Increased risk for formation of blood clots
  - Veins of the legs
  - Lungs
  - Other organs
  - Clots can be painful, damage organs and even be fatal

Ecluzumab (Soliris)

- Engineered antibody to complement proteins
  - Given intravenously every two weeks
- Prevents the complement from attacking red blood cells
- Patients receiving ecluzumab need fewer transfusions with about half not requiring any

Ecluzumab (Soliris, cont.)

- Effects on other aspects of PNH as well
  - Reduction in the number of abnormal blood clots by 92%
  - Effect on evolution to other diseases such as MDS and AML
- Definitely improves quality of life

Conclusions

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