Aplastic anemia and PNH: an overview

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Aplastic anemia
Diminished or absent hematopoietic precursors in the bone marrow
ANEMIA
THROMBOCYTOPENIA
LEUCOPENIA - NEUTROPENIA
Aplastic anemia

- Misnomer
  - Affects other cell types

- Rare disease
  - 2-4 patients per million per year

- Can be diagnosed at any age, in any race
Causes of AA

**Congenital**
- Fanconi anemia
- Dyskeratosis congenita
- Shwachman-Diamond syndrome
- Amegakaryocytic thrombocytopenia
- Reticular dysgenesis

**Acquired (80%)**
- Idiopathic (75%)
  - Drugs
    - Gold, NSAID, antiepileptic, antibiotics, anti-thyroid
  - Chemical exposition
    - Industrial chemicals, benzene, insecticides
  - Radiation exposition
  - Viruses
    - Parvovirus B19, HIC, hepatitis viruses
  - Immune disorders
  - Pregnancy
  - PNH
  - Anorexia nervosa
Clinical manifestations

- Anemia
  - Fatigue, dyspnea, cardiac problems

- Thrombocytopenia
  - Bleeding

- Leucopenia
  - Infection, fever
What causes idiopathic AA?
Immune-related bone marrow destruction
Evaluation and diagnostic

- Complete history
  - Medication review, specific exposure, known diseases
- Bone marrow aspiration and biopsy
Tests on the marrow

- Flow cytometry for PNH
- Cytogenetic analysis
Normal bone marrow biopsy

Bone marrow biopsy in AA

Normal bone marrow biopsy
Aplastic anemia severity

- Severity of cytopenias can be variable
  - Moderate
  - Severe
  - Very severe

- When is it severe or very severe
  - High risk of complications if no treatment given
  - High rate of mortality at 1 year if not treated (70%)
Indications for treatment

- Patients with severe and very severe AA require treatments
- Patients with non-severe AA will be followed and treated at progression
- Because of the prognosis if left untreated, treatment goal is to improve the long-term control of the disease
Treatment overview

- Remove the offending agent if needed
- Supportive treatment
  - Antibiotics for infection
  - Transfusions
- Definitive treatment
  - Immunosuppressive therapy
  - Allogeneic stem cell transplant
Treatment schema

Severe or very severe AA

≤ 40 yo

HLA identical sibling

yes

Transplant

no

> 40 yo

Immunosuppressive therapy (IST)

If no response
- 2nd course of IST
- unrelated donor transplant (depends on age)
Immunosuppressive therapy

- Modulates the body’s immune system
- Prevents the immune system from attacking the bone marrow stem cells
  - Cells can grow and blood counts improve
Immunosuppressive therapy

- Combination of
  - 1) Antithymoglobulins (iv x 5 days)
    - ATG produced by immunizing animals against human lymphoid tissue
  - 2) Cyclosporine (oral)
Immunosuppressive therapy complications

- Infusion reactions to the ATG
- Serum sickness
  - Rash, joint pain, fever, itchiness
- High blood pressure
- Kidney failure
- Gums swelling
- Unwanted hair
Immunosuppressive therapy

- Chances of response after 1st treatment (horse ATG)
  - Approximately 60-70% at 3-6 months

- Relapse in 30-40% of patients

- Chances of response after 2nd treatment (rabbit ATG)
  - 30% (range from 20-60% in different trials)
Elthrombopag (REVOLADE®)

- TPO agonist studied in patients with aplastic anemia refractory to IST
- 43 patients
  - 40% with improvement in their counts at 3-4-months
- REVOLADE® is indicated for the treatment of adult patients with severe aplastic anemia (SAA) who have had an insufficient response to immunosuppressive therapy (product monograph)
Survival determinants

- Age at diagnostic
- Severity of the disease
- Response to treatment
- Evolution of the disease

15% of AA patients will develop another hematologic condition:

- PNH
- MDS
- AML
Survival

Figure 2. Survival after response to immunosuppression in severe aplastic anemia. A large cohort (N = 243) of NIH patients who responded to treatment with the standard regimen of horse ATG plus cyclosporine was analyzed. Shown are long-term outcomes including the negative impact of a complicating event. Events were defined as relapse (need for further immunosuppression after protocol treatment) and clonal evolution (myelodysplasia/acute myeloid leukemia; almost always accompanied by a new cytogenetic abnormality in the BM). Approximately half of the patients did not experience a clonal event and poor survival was largely a consequence of disease progression. Data were censored for transplantation.¹
Conclusion

- Idiopathic aplastic anemia is a failure of bone marrow stem cells caused by an immune attack
  - Many other causes
- It can affect all blood cells
- Can be severe and needs treatment
- Effective treatments are available
PNH
What is PNH?

- Rare disease
  - 1-5 people affected per million population
- Main problem is red cells destruction in the circulation (hemolysis)
  - Gives rise to many problems...

Source: soliris.net

What is PNH?

- Chronic and severe disease
  - Life long disease
  - Many organs can be affected

- Life threatening
Figure 2. Actuarial Survival from the Time of Diagnosis in 80 Patients with PNH.

The median survival was 10 years. The expected survival of an age- and sex-matched control group is shown for comparison.
What does PNH mean?

- **Paroxysmal** = sudden recurrence

- **Nocturnal** = at night

- **Hemoglobinuria** = presence of free hemoglobin in the urine
  - Resulting from destruction of red cells (hemolysis)
Clinical manifestations

- Anemia (hemolysis)
  - Fatigue, shortness of breath
- Thrombosis (venous or arterial)
- Others
  - Fatigue
  - Abdominal pain, oesophageal spasm
  - Chronic kidney disease
  - Pulmonary hypertension
  - Erectile dysfunction
- Bleeding, infection
  - In case of associated marrow failure
Clinical manifestations

- Anemia
  - Fatigue
- Thrombosis
- Others
  - Fatigue
  - Abdominal pain, esophageal spasm
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- Bleeding, infection
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Impact on quality of life
What causes PNH?

- Mutation in the PIG-A gene, located on the X chromosome
  - Has to be there to produce a normal protein
  - Protein is implicated in the formation of a molecule (GPI-anchor)
- Acquired mutation
  - Not hereditary

Source: Blood Journal and nature.com
What causes PNH?
What causes PNH?

Relationship with red cells destruction (hemolysis)??

Source: nature.com
- Membrane attack complex (MAC)
  - Part of the complement system, an important component of our immune system
  - Create holes in the cells membrane
  - Role is to destroy dead cells, foreign body
  - Can also destroy good cells
Hemoglobin
NORMAL INDIVIDUAL

- Hemoglobins
- MAC Protectors (proteins)
- GPI anchor
PNH PATIENTS

Unable to protect red cells against MAC

Free Hemoglobin
Consequences of hemolysis

- Anemia
  - Fatigue
  - Dyspnea
- Jaundice
- Dark urine coloration
- Iron and folic acid deficiency
- High LDH levels
Nitric oxide (NO) depletion

- Vasoconstriction
- Platelet activation
- Smooth muscle contraction
Clinical manifestations of NO depletion

- Fatigue
- Abdominal pain, esophageal spasm
- Chronic kidney disease
- Pulmonary hypertension
- Erectile dysfunction
Thrombosis

- Leading cause of death
  - Presenting symptom in 5%
  - Occurs in up to 40% during disease evolution
- Can affect both venous and arterial system
- Atypical locations
  - Hepatic, portal, mesenteric, cerebral, dermal
    - Abdominal pain
    - Cirrhosis
- Treated with anticoagulant
How is PNH diagnosed?
Flow cytometry

- The most important test for diagnostic
- Done on a peripheral blood specimen
- Identifies ≥2 cell lineages with absent or decreased GPI-AP
- Helps to predict severity of disease
What are treatment options?
Treatment options

- Supportive treatments
  - Iron supplements
  - Folic acid supplements
  - Transfusions
  - Anticoagulation if thrombosis

- Disease modifying treatments
  - Anti-complement therapy (Eculizumab)
  - Allogeneic transplant
Indications for anti-complement therapy

- Severe fatigue
- Thrombosis
- Transfusion dependency
- Symptoms of muscle dystonia (pain)
- Other organ damage
Eculizumab inhibits C5 in the complement system and prevents the formation of the MAC
PNH PATIENTS

Free Hemoglobin
Hemoglobin
Eculizumab efficacy: LDH levels

NEJM 2006;355:1233
Eculizumab efficacy: Transfusion needs

Open-label extension study

British Journal of Haematology, 2013, 162, 62–73
Eculizumab efficacy

- Reduces
  - Hypercoagulability (thrombosis)
  - Smooth muscle dystonia
  - Stabilize or improve kidney function
  - Improve quality of life (fatigue)

- Long term treatment (needs to be given regularly to be effective)
Effect on survival

Fig 4. Long-term survival with eculizumab therapy.
Effect on survival

Figure 1 Kaplan-Meier survival plots depicting PNH patients on eculizumab compared to age and sex matched controls.
Eculizumab administration

- 600 mg iv once per week x 4
- 900 mg iv one week later
- 900 mg iv every 2 weeks
- Indefinitely

- Monitoring
  - CBC, LDH, reticulocytes
  - Will help to adjust dose and interval between treatments
- Patients needs vaccination against *Neisseria meningitidis*
Allogeneic stem cell transplant

- Is the only curative therapy
- Higher potential for toxicities (short and long term)

Indications
- PNH unresponsive to eculizumab
- Severe aplastic anemia
- High-risk myelodysplastic syndrome
Conclusion

- PNH is a rare and severe acquired disease affecting many organs
- Decreases life expectancy and affects quality of life
- Exist treatments to overcome symptoms and improve survival