Severe Congenital Neutropenia

Genetics

– Most common: Dominant mutations in the neutrophil elastase (*ELANE*) gene

– Rare: Dominant and recessive mutations of other genes (e.g. *G6PC3, HAX1, GFI1, WAS, JAGN1, VPS45, CSF3R*)

– Only *HAX1* = “Kostmann syndrome”

– Most mutations in the G-CSF receptor gene (*CSF3R*) are acquired and may be preleukemic
Mechanism of neutropenia in SCN

Increased cell death ("apoptosis") in bone marrow precursors
Neutrophil development
Cell death in SCN
Treatment

Definitive therapy:

• G-CSF (filgrastim, Neupogen®)

• Hematopoietic stem cell transplantation
Risks of sepsis and of myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML)

After 10 years on G-CSF, 21% developed myelodysplasia and/or AML

After 10 years on G-CSF, 8% had died of sepsis.

Rosenberg et al. Br J Haematol 2010; 140:210
Risk of Sepsis

Prior to G-CSF: ~100%
Since G-CSF: ~8% over 10 years
Why isn’t it 0?
• Non-responders
• Non-adherence
• Undetected MDS/AML
• Impaired neutrophil function?
Relative Risk of MDS/AML
Role of G-CSF Response

<table>
<thead>
<tr>
<th>G-CSF dose</th>
<th>ANC ≥ 2188</th>
<th>ANC &lt; 2188</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 8µg/kg/day</td>
<td>1.0</td>
<td>1.7 (0.5-6.4)</td>
</tr>
<tr>
<td>≥ 8µg/kg/day</td>
<td>1.7 (0.5-5.5)</td>
<td>4.5 (1.5-13.4)</td>
</tr>
</tbody>
</table>

p=0.008

Rosenberg et al., Blood 2006; 107: 4628
Comparison of Highest and Lowest Risk Groups

Cumulative Incidence at 10 years
High risk group: 40%      Low risk group: 11%
Symptoms of MDS/AML

• Persistent fever (↓ white cells)
• Paleness, fatigue, shortness of breath (↓ red cells)
• Easy bruising, bleeding (↓ platelets)
• All of the above
• None of the above – hence need for monitoring
Monitoring for MDS/AML

Yearly bone marrow examination
• Cell number and distribution: evidence of leukemia?
• Cytogenetics (chromosomes): changes predictive of MDS/AML? e.g. monosomy 7

Regular blood counts
• Loss of response to G-CSF
• Decreased red cells or platelets

} Consider bone marrow exam
Indications for Transplant

Highly recommended
• MDS/AML
• MDS-associated cytogenetic abnormality
• No response to G-CSF

Possibly recommended
• High dose of G-CSF required for ANC still <2000
• ELANE mutation with high risk of MDS/AML (?)
• Intolerable side effects of G-CSF

Probably not recommended
• Doing well on low dose G-CSF

Also depends highly on availability & type of donor