

Factory Closures, Defective Goods, and Lack of Skilled Workers

Problems for the bone marrow and the global economy

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Preview

• What does your bone marrow do?

• Why does it fail?

• What can we do about it?











Blood is not forever

- Blood cell lifespans:
 RBC: 4 months
 PIt: 5 days
 WBC: 24 hours
- Normally there is less than 5% variation in blood counts



The bone marrow works constantly to maintain balance



It's all about supply and demand

Demand is too high

• e.g. bleeding

Supply is too low

- Bone marrow failure
 - Aplastic anaemia

Supply

- PNH
- MDS



It's an unregulated free-market economy... What could go wrong?





How can a factory fail?







How can a factory fail?

- It may be abandoned.
 Aplastic anaemia
- 2. It may begin to ship defective goods. Paroxysmal nocturnal haemoglobinuria
- 3. It may lose its ability to produce high quality product.

Myelodysplastic syndrome









What is Aplastic Anaemia?

- <u>Rare</u>: 5 cases per million per year
- Stem cells are lost/destroyed due to immune system, toxins, or inherited problems
 - The bone marrow cannot meet the body's needs for new blood cells
 - Anaemia
 - Low platelet count
 - Low white blood cell count





Paroxysmal Nocturnal Haemoglobinuria The Goods are Defective





Where does the name "PNH" come from?

The origin of the name PNH



Why is there haemoglobin in this patient's urine?



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In PNH, their most vital organ is exploding.



What is PNH?



- Extremely rare: 1-2 cases per million per year
- Often goes with AA or MDS
- Stem cell mutation in *PIGA*
- Leads to loss of the "GPI anchor"
 RBC vulnerable to lysis by complement







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Myelodysplastic Syndrome Lack of Skilled Workers



"I had to let the new lad go he kept chuckin' out the bent ones."

- <u>Too much</u> quality control!
- Bone marrow is working hard.
 - Most blood cells are defective – not exported to the blood.





What is MDS?

- 50-100 per million per year
- Causes: radiation, chemo, organic solvents
 - <u>Usually</u> cause is unknown
- Blood cells develop abnormally
 - Prevented from entering blood by <u>overly</u>
 <u>vigilant quality control</u>







What is MDS?

- Ineffective Haematopoiesis
- reduction of peripheral blood counts
- normal or increased bone marrow cellularity
- "dysplasia"

• **Propensity** to evolve into AML



MOST



Healthy



PNH













Approaches to Treatment for Bone Marrow Failure







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- 'First aid' for bone marrow failure
- Makes sense!
 - ...but many drawbacks
 - Iron overload
 - Infection
 - Heart failure
 - Inconvenience





Provide incentives to the workers.



"Have a nice day, Dear."



Provide incentives to the workers Growth Factors

- Bone marrow stimulated to make more blood cells
- In MDS: sometimes an excellent temporary fix
 - Eprex, aranesp, neupogen
- AA, PNH: You can't stimulate what isn't there!



"Have a nice day, Dear."



Results with growth factors

• MDS

- Epo/G-CSF 'first
 line' Rx in low-risk
 MDS
- Up to 50% respond
- Responses last 12 years

- AA and PNH
 - No role as sole
 Rx
 - With IST: may increase risk of MDS



Improve working conditions



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brook

Improve working conditions Immunosuppressive Therapy



- In AA (and PNH, and MDS) the immune system attacks bone marrow cells
- Suppressing the immune system often helps
 - Antithymocyte globulin
 - Cyclosporine



Results with

immunosuppressive therapy

- Aplastic anaemia
 - 70-80% response
 - ~90% if there is a PNH clone detectable
- PNH
 - No big studies

- MDS (low-risk)
 - 50-60% response
 - More likely to respond if:
 - Hypoplastic variant
 - Certain HLA types
 - Younger
 - Fewer transfusions

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The Ronald Reagan Approach

Fire all the workers and replace 'em!

speaks out against SOCIALIZED MEDICINE





speaks out

against

SOCIALIZE

MEDICINE

MOST

 Potential CURE in all three diseases

defective bone marrow

• Very harsh!



Results with BMT

• MDS

- -~30% cure rate
- Relapse rate is high
- Works better for low-risk than for high-risk MDS

• AA

- Up to 90% cure rate
- PNH
 - Reserved for 'last resort'





Retrain the workers





Retrain the workers Hypomethylating Agents

- Drugs that modify chromatin
 - Vidaza

LEARN?

- dacogen
- Malfunctioning stem cells can be reprogrammed



Results with hypomethylating agents

In MDS:

- Improved blood counts
- Fewer transfusions
- Improved QoL
- Less leukaemia
- Longer survival (Vidaza)

In AA and PNH:

- Nothing
- You can't retrain an empty factory...



Throw out the troublemakers



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Throw out the troublemakers Revlimid

- In del(5q) MDS
- Gets rid of the MDS cells
- Transfusion independence in 70%
- Nobody knows how!



MOST







Bassett's is recalling all bags of its 'Milky Babies'. Due to a fault in the manufacturing process, some bags may contain small pieces of solid material which could pose a choking hazard.

If you have bought this product, please return the bag for a full refund to: Bassett's Recall, Freepost MID 20061, Birmingham B30 20Z

Or ring our Helpline number on 0800 818181

This action has been taken as a precautionary measure.

No other Bassett's products are affected.

Bassett's would like to apologise to all our customers for any inconvenience caused.





Issue a product recall Soliris in PNH



• In PNH the RBC are fragile and don't last long

 If we can't replace or retrain the RBC, can we offer a fix that lets them last longer?





Soliris protects PNH cells by blocking complement





Results with Soliris

Anaemia

- Immediate and sustained reduction in haemolysis
- 50% of patients become transfusionindependent
- Fatigue reduced
- Quality of life improved
- Thrombosis reduced





Problems with Soliris

- Increased risk of severe meningiococcal infection
- Cost: US\$389,000/year (wholesale)







Defective product





Empty factory



Lack of skills





Thank you.

