THE MDS MAP

Where Are We and Where Are We Going?

Outline

- The Globe (marrow function)
- The Region (disorders of blood cell development)
- My Town (defining myelodysplasia)
- My Neighbourhood (classification of myelodysplasia)
- How Did I Get Here (development of myelodysplasia)
- Traffic, Detours and Fast Lanes (treatment options)
- The Journey (understanding prognosis)

The MDS Map The Globe (marrow function)



The Globe



The Globe



The Region (disorders of blood cell development)



The Region

- CHIP (clonal hematopoiesis of indeterminate potential)
- ICUS (idiopathic cytopenias of uncertain significance)
- MDS (myelodyplastic syndromes)
- MPN (myeloproliferative neoplasms)
- AML (acute myelogenous leukemia)
- AA (aplastic anemia)
- PNH (paroxysmal nocturnal hemoglobinuria)

The Region

	Marrow cells	Blood cells	Differentiation	Clonal
CHIP	Normal	Normal	Normal	Yes
ICUS	Normal	\downarrow	Normal	?
MDS	Usually ↑	\downarrow	Abnormal	Yes
MPN	1	1	Normal	Yes
AML	Usually ↑	↑ or ↓	Absent	Yes
AA	\downarrow	\downarrow	(Normal)	?
PNH	Normal or \downarrow	Normal or \downarrow	(Normal)	Yes

The Region



My Town (definition of MDS)

- Morphologically abnormal differentiation of one or more cell lines
- Other causes ruled out (eg. drugs, toxins)

My Neighbourhood (classification of MDS)

Normal or increased myeloblasts



- Normal or increased myeloblasts
- Unilineage or multilineage dysplasia

- Normal or increased myeloblasts
- Unilineage or multilineage dysplasia
- Presence or absence of ringed sideroblasts



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- Normal or increased myeloblasts
- Unilineage or multilineage dysplasia
- Presence or absence of ringed sideroblasts
- Presence or absence of del(5q)







How Did I Get Here (development of MDS)

Genetic damage to stem cell



How Did I Get HereThe DNA code



- How Did I Get Here
 - Copying of message (transcription)

start by making xpod kntuy whna hammer from dypoe jkev wood and iron.

How Did I Get Here

Removal of introns (splicing)

start by making xpod kntuy whna hammer from dypoe jkev wood and iron.

start by making a hammer from wood and iron.

How Did I Get Here

Production of protein (translation)

start by making a hammer from wood and iron.



- Genetic damage to stem cell
 - Causes
 - Chemical
 - Drugs (eg. Chemo)
 - Radiation
 - Random
 - Outcomes
 - Repair
 - Cell death
 - Altered cell physiology

- Altered cell physiology
 - Cells have "back-up" systems single abnormality less likely to affect cell function
 - Development of single gene mutations increases with age - CHIP detected in about 10% of those >80
 - Mutated cells may be more prone to further damage

- Altered cell physiology
 - Genes affected
 - Chromatin modification (turning on and off genes)
 - DNA methylation (turning on and off genes)
 - RNA splicing (editing of RNA message)
 - DNA repair
 - Transcription (copying genetic code into message for protein production)
 - Driver mutations
 - Cooperating mutations

- Altered cell physiology
 - Genetic instability
 - Chromosomal damage
 - MDS stem cell
 - Survival advantage (gradually replaces normal stem cells)
 - Abnormal development (ineffective marrow function)
 - Increased likelihood of further genetic damage (development of AML)

Traffic, Detours and Fast Lanes (treatment options)

- Cure
- Improve function/slow progression
- Support

- Cure
 - Stem cell transplant
- Improve function/slow progression
 - Lenalidomide
 - Azacitidine
- Support
 - Transfusion
 - Growth factors
 - Other

- Stem cell transplant
 - Replacement of abnormal (and normal) stem cells by donor stem cells
 - Limitations
 - Donor availability
 - Toxicity

- Traffic, Detours and Fast Lanes
 - Stem cell transplant
 - Donor availability
 - Matched sibling
 - Matched unrelated (ethnicity dependent)
 - Haploidentical (siblings, parents, children)
 - Toxicity
 - Conditioning regimen (preparing the recipient)
 - "nuclear option" vs "establish beach head"
 - Graft vs host disease
 - Donor source
 - Age/comorbidities

- Improve function/slow progression
 - Lenalidomide
 - Limited to those with del(5q)
 - How it works ?

- Improve function/slow progression
 - Azacitidine



- Support
 - Transfusions
 - Red cells
 - Iron overload
 - RBC antibodies
 - Platelets
 - Short life-span
 - Platelet antibodies

- Support
 - Growth factors
 - Erythropoietin
 - Limited use
 - Expensive
 - Filgrastim
 - Double edge sword
 - Thrombopoietin agonists

The Journey (prognosis)

- Disease factors
 - Blast #
 - Severity of cytopenias
 - Cytogenetic/molecular abnormalities
- Patient factors
 - Age
 - Coexisting health issues

The Journey

- Prognostic scores
 - International prognostic scoring system (IPSS)
 - Marrow blast%, karyotype, number of cytopenias
 - Revised IPSS (IPSS-R)
 - Age, marrow blast%, karyotype, severity of anemia/neutropenia/thrombocytopenia
 - WHO (WPSS)
 - WHO category, karyotype, transfusion requirement

The Journey



Where Next?

- Improved stem cell transplant
- Conversion of molecular knowledge into treatment targets (personalized medicine)