New and Emerging Therapies for Myelodysplastic Syndromes

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Myelodysplastic Syndromes - MDS

- Bone marrow cancers characterized by dysplasia, clonality, and ineffective hematopoiesis
- Disease of older individuals
- Slightly more common among men than women
- Survival varies months to years depending on subtype
MDS is a spectrum of diseases

Type and Maturity of Blood cells

- MDS-SLD
- MDS-RS
- MDS-MLD
- MDS-del(5q)
- MDS-EB1
- MDS-EB2
- MDS-U

Variation in Blood Counts

Variation in Driver Mutations

MDS treatment is based on disease risk

Risk Stratification by IPSS or IPSS-R
Blood Counts, Blasts, and Karyotype

Risk of Serious or Life-threatening Complication related to MDS:
  *Infection*
  *Bleeding*

Risk of Progression to Acute Myeloid Leukemia

*IPSS and IPSS-R Risk do not always match the risk of the WHO disease subtype*
Updates in Estimating Disease Risk

• New understanding about mutations in MDS
• Competing risks in often older patients
• Changes in MDS risk over time
Recurrent Somatic Mutations

Common Mutations:
- SF3B1 – ringed sideroblasts
- TET2
- SRSF2
- ASXL1
- DNMT3A
- RUNX1
- U2AF1
- TP53
- EZH2
- IDH2
- STAG2
- ZRSR2
Mutations are common – and not all MDS!

Mutations add to diagnosis and prognosis (and treatment?)

- **MDS**
- **MPN**
- **BMF**
- **Therapy**
- **Healthy**
- **Baseline Hematopoiesis**
- **Clonal Hematopoiesis**
- **Linear Evolution**
- **Branching Evolution**

**Secondary AML**

**De novo AML**
Mutations in Healthy Persons and Heart Disease

Competing Risks in MDS

Proportion of deaths attributed to MDS/Leukemia, CVD, and Other Causes

Time of death from diagnosis:
- <= 12 months (n=8836)
- 12-36 months (n=7118)
- 36-60 months (n=2988)
- >60 months (n=2430)

Proportion of Deaths (%)

- MDS/Myeloid Leukemia: 50.8% (5.8), 48.4% (4.8), 39.1% (3.9), 20.5% (2.0), 16.7% (1.7), 18.4% (1.8), 22.2% (2.2), 26.9% (2.7), 32.5% (3.2), 33.2% (3.3), 38.7% (3.9), 43.7% (4.4)
- CVD: 50.8% (5.8), 48.4% (4.8), 39.1% (3.9), 20.5% (2.0), 16.7% (1.7), 18.4% (1.8), 22.2% (2.2), 26.9% (2.7), 32.5% (3.2), 33.2% (3.3), 38.7% (3.9), 43.7% (4.4)
- Other: 50.8% (5.8), 48.4% (4.8), 39.1% (3.9), 20.5% (2.0), 16.7% (1.7), 18.4% (1.8), 22.2% (2.2), 26.9% (2.7), 32.5% (3.2), 33.2% (3.3), 38.7% (3.9), 43.7% (4.4)
Disease Risk: Fixed or Fluctuating?

A

IPSS-R (hazard plot)

Monthly mortality (vhrl) shortly after diagnosis (~10%)

monthly mortality total after ~2.5 years (~5%)

pts. at risk

very low 1355 967 632 377 224 138 78
low 2723 1730 1054 599 322 175 97
int 1470 767 386 193 99 56 34
high 927 345 125 70 37 23 16
very high 737 124 36 15 8 5 2

B

overall survival by IPSS-R

Estimated proportion surviving

pts. at risk

very low 1355 1355 1304 1238 1195 1161 1121 1083
low 2723 2723 2591 2459 2349 2250 2142 2052
int 1470 1470 1396 1292 1200 1120 1037 960
high 927 927 835 749 668 586 533 482
very high 737 736 592 472 372 304 245 203

MDS Diagnosis

Lower Risk Disease
Low/INT-1
- Good QOL, no transfusions
  - Follow CBC
- Single Cytopenia
- Multiple Cytopenias
  - Transfuse/Growth Factor
  - CsA/ATG
  - HMA or Lenalidomide

Higher Risk Disease
(INT-2/High or IPSS-R > 4.5)
- HCT Candidate
- HMA Induction
- Allo-HCT
- Not HCT Candidate
  - HMA Induction Clinical Trial

Risk Stratification

- Poor response/High IPSS-R
  - ?High risk mutations
MDS Management

**MDS Diagnosis**

**Lower Risk Disease**
- Low/INT-1

**Higher Risk Disease**
- (INT-2/High or IPSS-R > 4.5)

**Risk Stratification**

**MODIFY SYMPTOMS**
- Good QOL, no transfusions
- Single Cytopenia
- Multiple Cytopenias
- Follow CBC
- Transfuse/Growth Factor
- CsA/ATG

**HMA or Lenalidomide**

**MODIFY DISEASE**

**Risk of Death and AML**
- Candidate
  - HMA Induction
  - Allo-HCT
  - HMA Induction
  - Clinical Trial

**Transfusion Dependence**
- Transfusion Dependence

**Poor response/High IPSS-R**
- ? High risk mutations

**MODIFY DISEASE**

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**Risk Stratification**

- HCT Candidate
- Not HCT Candidate

**HMA Induction**

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**Follow-up**

- Single Cytopenia
- Multiple Cytopenias

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**Clinical Trial**

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**Lower Risk Disease**

**Not HCT Candidate**

**HMA Induction**

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**HMA Induction**

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**Allo-HCT**

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**Clinical Trial**

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**HMA Induction**

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**HMA Induction**

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**Clinical Trial**

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**HMA Induction**

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**Clinical Trial**

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**HMA Induction**

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**Clinical Trial**

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MDS Management

Lower Risk Disease
Low/INT-1

Good QOL, no transfusions

Single Cytopenia

Follow CBC

Multiple Cytopenias

Transfusion Dependence

Specific Cytopenia

EPO Level

Neutropenia

HMA or Lenalidomide

CsA/ATG

 MODIFY SYMPTOMS

Transfusion Dependence

5q- Syndrome

Transfusion Dependence

Hypoplastic MDS/AA

5q- Syndrome

EPO Level

Neutropenia

Hypoplastic MDS/AA
MDS Management

More Immediate Risk of Death Due to Disease or AML

Transplant Candidacy

Chemotherapy

 MODIFY DISEASE
 Risk of Death and AML

Higher Risk Disease (INT-2/High or IPSS-R > 4.5)

HCT Candidate

Not HCT Candidate

HMA Induction

Allo-HCT

AML

Induction

Clinical Trial

MDS Management
MDS Management – Integrating Many Factors

- AML Risk
- "Targetable" Mutations
- Transfusion Needs
- Toxicity Profile
- Travel
- Time
Therapeutic Targets in MDS
New Therapies to Target MDS

- **Pathway Driven**
  - TGF-β pathway
  - Immune Checkpoint Blockade
  - Apoptosis – Bcl2

- **Mutation Driven**
  - Spliceosome mutations
  - Mutated IDH enzymes
New Therapies to Target MDS

• Pathway Driven
  • **TGF-β pathway**
  • Immune Checkpoint Blockade
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• Mutation Driven
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TGF-B Ligand Traps and Erythropoiesis

Blank U and Karlsson S. Blood 2015 125:3542-3550

Luspatercept

- Activin receptor IIIB protein, TGFB family member ligand trap
- EPO >500 or intolerant of ESAs, no prior HMA
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• Mutation Driven
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Immune Checkpoints in Cancer

Pardoll DM. Nature Reviews Cancer 2012;12, 252-264
DNMTI and Interferon Response

- increased expression of endogenous retroviral transcripts (ERVs)
- increases dsRNA
- CTLA-4 + AZA synergistic in a mouse melanoma model
PD-L1 in MDS

- PD-L1 is upregulated in MDS blasts after exposure to IFNγ and TNFα


Proliferative MDS cells are PD-L1+
New Therapies to Target MDS

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  • Apoptosis – Bcl2

• Mutation Driven
  • Spliceosome mutations
  • Mutated IDH enzymes
Apoptosis in MDS

• BCL2 is a regulator of apoptosis
• “priming” apoptosis may be attractive in treating MDS
New Therapies to Target MDS

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  • Apoptosis – Bcl2

• Mutation Driven
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  • Mutated IDH enzymes
Spliceosome mutations in MDS

Joshi et al. Blood 2017 129:2465-2470
Possible Spliceosome Targets

New Therapies to Target MDS

• Pathway Driven
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• Mutation Driven
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  • Mutated IDH enzymes
Targeting mutated IDH proteins

Cellular Metabolism Proteins: IDH1 and IDH2

Mitochondria in cell cytoplasm

Citric acid cycle or "Krebs Cycle" Enzyme reactions that occur in mitochondria

Cell membrane

Conclusions

• Our understanding of MDS has grown significantly
• This knowledge may help us to identify new targets for treatment
• A number of therapies are in development and have exciting potential
• New targets continue to be identified

• Questions? abrunner@partners.org