MDS: Navigating Lower Risk Disease

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Standard Treatment Options

- Observation
- Erythropoiesis-Stimulating Agents (Growth Factors)
- Immunosuppressive Therapy
- Lenalidomide
- Hypomethylating Agents
Observation

• Not all patients need active therapy for MDS
  • Mildly low blood counts
  • No need for transfusions
  • No/few symptoms

• “Watchful Waiting”

• Treating lower-risk patients early has NOT been shown to improve outcomes
Erythropoietin

Low $O_2$

Liver

Kidneys

$\uparrow O_2$ carrying capacity

Epo

Bone

Blood cells
Erythropoiesis Stimulating Agents

- 30-40% response rates in patients with anemia

- Epoetin alfa (Procrit) and darbepoetin (Aranesp) are likely equally effective

- Addition of G-CSF (stimulates white blood cell production) may be helpful
Factors associated with response:

- Low serum (endogenous) erythropoietin level
- Low transfusion dependence (<2 units/month)

<table>
<thead>
<tr>
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<th>Response Rate</th>
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<tbody>
<tr>
<td>Neither Factor</td>
<td>7%</td>
</tr>
<tr>
<td>1 Factor</td>
<td>23%</td>
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<tr>
<td>Both Factors</td>
<td>74%</td>
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Hellström-Lindberg E, Br J Haematology 2003
Caution with ESAs

- Linked to increased heart attacks, stroke, blood clots, tumor growth, and death in patients with solid tumors

- This HAS NOT been shown in patients with MDS
Immune-Mediated Destruction

- Insult
- Cytotoxic T cells
- Expansion

Suppression of blood stem cells
Anti-Thymocyte Globulin & Cyclosporine

- Kill and block activity of T cells, restoring blood production

- Response rate ~30%

- Possible side effects: Allergic reactions, serum sickness, increased risk of infections, kidney dysfunction, neurologic issues

Passweg JR, JCO 2010
Favorable factors for response:

- Young Age
- Immune receptor type (HLA-DR15)
- Low cellular marrow
- Ratio of T-cell subtypes (Low CD4:CD8)
- PNH clones
Lenalidomide

- Oral capsule taken daily
- Improves anemia in patients with lower-risk disease and del(5q)

<table>
<thead>
<tr>
<th></th>
<th>All patients (n=148)</th>
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<tbody>
<tr>
<td>Red Blood Cell Response</td>
<td></td>
</tr>
<tr>
<td>Transfusion Independence</td>
<td>67%</td>
</tr>
<tr>
<td>≥50% decrease in transfusions</td>
<td>9%</td>
</tr>
<tr>
<td>Total Transfusion Response</td>
<td>76%</td>
</tr>
<tr>
<td>Average Time to Response (weeks)</td>
<td>4.6</td>
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- Often causes decreased neutrophils and platelets

Iron Balance

Daily intake: 1-2 mg

Potential long-term complications:
- Heart failure
- Liver disease
- Diabetes
- Skin changes
- Endocrine/hormone dysfunction

Daily losses: 1-2 mg

~250 mg/unit
Iron Chelation Therapy

• Deferasirox decreases serum ferritin but high discontinuation rates

• Considered in patients with:
  • Lower-risk disease with long life expectancy
  • Serum ferritin (measure of iron stores) greater than 1,000-2,500 mcg/L or other evidence of iron overload
DNA Methylation

Hypomethylation

Promotor → Methyl-OH → Promotor

Hypermethylation

Promotor → Methyl → Promotor

Promotor → Genes

Genes → Promotor

Genes → Methyl → Genes
Hypomethylating Agents (HMAs)

- IV or subcutaneous administration, 5-7 days each month
- Outpatient therapy
- May take several cycles before response is seen
- Therapy should be continued indefinitely, even in patients who respond

5-Azacitidine

Decitabine
3 Alternative Dosing Schedules of Azacitidine

- May also improve platelets and/or neutrophils

Lyons, et al., J Clin Oncol 27:1850-6, 2009
Newly Diagnosed MDS

Risk Stratify

Lower-risk disease

Symptomatic or transfusion dependent

No

Yes

Observation

Predominantly anemic

Yes

No

Favorable characteristics for IST

Yes

No

Higher-risk disease

HMA

Lenalidomide

Low Epo < 2 U RBC/mo

Favorable characteristics for IST

Yes

No

ESA ± G-CSF

Favorable characteristics for IST
Recent Advancements in Lower-Risk Disease
Luspatercept

TGF-β superfamily ligand

ActRIIB

P

Smad2/3

Complex

Cytoplasm

Nucleus

Red Blood Cell Maturation

ESAs  Luspatercept

Fenaux P, et al. ASH 2018, Abstract #1
Luspatercept

- Phase 3 study in lower-risk patients with MDS with Ring Sideroblasts, after erythropoiesis-stimulating agents

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<thead>
<tr>
<th></th>
<th>Luspatercept</th>
<th>Placebo</th>
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<tbody>
<tr>
<td>Red Blood Cell Transfusion</td>
<td>37.9%</td>
<td>13.2%</td>
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<tr>
<td>Independence ≥ 8 Weeks</td>
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- Granted priority review by the FDA
- *May* be approved as early as April 2020
Eltrombopag

- Oral drug that stimulates platelet production
- Associated with decreased blasts in preclinical models
- Currently FDA approved for immune thrombocytopenia, aplastic anemia
Eltrombopag

<table>
<thead>
<tr>
<th>At 12 weeks:</th>
<th>Eltrombopag</th>
<th>Placebo</th>
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<tbody>
<tr>
<td>Platelet Responses</td>
<td>47%</td>
<td>3%</td>
</tr>
<tr>
<td>Disease Progression</td>
<td>7%</td>
<td>3%</td>
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- Some improvement in red blood cells and/or neutrophils was seen in a subset of patients
- **NOT** FDA approved
- Black-box Warning: May worsen disease in patients also on azacitidine