What are Growth Factors?

- Usually refers to erythropoiesis stimulating agents (ESAs):
  - Erythropoietin (Procrit)
  - Darbepoietin (Aranesp)

- Can also refer to granulocyte (macrophage) colony stimulating factors:
  - G-CSF (Neupogen)
  - GM-CSF (Leukine)

How do GF work?
Bone Marrow Basics

- Stem Cells
- Bone Marrow
- Blood Stream
- EPO
- Red Blood Cells
- White Blood Cells
- Platelets

Bone Marrow Basics (II)

- Red Blood Cells
- Oxygen
- Tissues (Heart, Liver, Kidneys)
- White Blood Cells
- Platelets
- Infection
- Wound

MDS in the Bone Marrow (I)

- Stem Cells
- Bone Marrow
- Blood Stream
MDS in the Bone Marrow (II)

Stem Cells → Bone Marrow

Red Blood Cells, White Blood Cells, Platelets → Blood Stream

MDS in the Bone Marrow (III)

Stem Cells → Bone Marrow

Cytokines

Red Blood Cells, White Blood Cells, Platelets → Blood Stream

MDS in the Bone Marrow (III)

Cytokines

EPO

Red Blood Cells, White Blood Cells, Platelets → Blood Stream
Who should get treated with GF?

• **Lower Risk** (OS 3-10 years, low rate AML)
  - RA, RARS
  - RCUD, RCMD
  - MDS-U, MDS del (5q)
  - IPSS Low, Int-1 (0-1.0)

• **Higher Risk** (OS <2 years, high rate AML)
  - RAEB (-1, -2)
  - IPSS Int-2, High (> 1.5)

---

How Many MDS Patients Require Transfusions?

In an on-line survey of 358 MDS Patients through the AAMDS...

- 82% had anemia
- 46% had thrombocytopenia
- 45% had neutropenia
- 65% had received a blood transfusion
  - 52% within the past 3 months
  - 27% at the time of the survey

Sekeres et al. Blood 2009

Blood Transfusions... the Bad

- Time-consuming
- Costly
- Small but real infection risk and associated fears
- Risk of transfusion reaction (febrile, allergic)
- Alloimmunization
- Each unit of blood carries ~250 mg elemental iron

Slide courtesy D. Steensma

...and the Worst, In MDS

Cumulative Probability of Survival among 374 MDS Patients in Pavia, Italy, 1992–2002 (transfusion hazard ratio for death, 1.58; P=0.005).

How are MDS Patients Treated in the U.S.?

Therapy in MDS (I)

Squeeze every last ounce of production out of the remaining functional stem cells with Erythropoietin Stimulating Agents (ESAs) and Growth Factors (GFs)

ESAs/GF in MDS: Who Responds?

**Score > +1**
- Broad response (74%, n=34)

**Score = -1 to +1**
- Intermediate response (23%, n=31)

**Score < -1**
- Poor response (7%, n=29)

<table>
<thead>
<tr>
<th>Treatment response score</th>
<th>Score &gt; +1</th>
<th>Intermediate response (23%, n=31)</th>
<th>Poor response (7%, n=29)</th>
</tr>
</thead>
<tbody>
<tr>
<td>s-epo</td>
<td>&lt;100</td>
<td>+2</td>
<td></td>
</tr>
<tr>
<td>U/mL</td>
<td>100-500</td>
<td>+1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;500</td>
<td>–3</td>
<td></td>
</tr>
<tr>
<td>Transf</td>
<td>&lt;2 units/m</td>
<td>+2</td>
<td></td>
</tr>
<tr>
<td>U RBC/m</td>
<td>&gt; or =2 units/m</td>
<td>–2</td>
<td></td>
</tr>
</tbody>
</table>


**Treatment response score**

**ESA/GF for Low-risk MDS**


---

**Median Response Duration of 129 MDS Patients to Epo Plus G-CSF**


---

**Survival: GF vs. NGF**

How do we decide who should receive GF and who should be treated with other MDS drugs (NGF)?

Deciding The Best Treatment for Low-risk MDS

- Decision analysis of 799 low-risk MDS patients
  - 394 treated with GF
  - 405 treated with NGF
- Patients reclassified by IPSS, using IWG response criteria, and divided into 3 GF predictive groups
- Response rates, survival, QOL included
Deciding The Best Treatment for Low-risk MDS

Low-risk MDS Patient Diagnosed (IPSS score 0-1.0)
Assess Txf Needs and Epo Level

Assign Predictive Group

- Low Transfusion needs
- Low Epo Level
- Intermediate
- (Chance of Responding to GF = 23%)
- High Transfusion Needs
- High Epo Level
- Poor
- (Chance of Responding to GF = 7%)

GF NGF
Response to NGF must be >46% to choose NGF
Response to NGF must be >14% to choose NGF
Response to NGF must be >4% to choose NGF

Deciding The Best Treatment for Low-risk MDS

GF Predictive Group

<table>
<thead>
<tr>
<th>Initial Treatment</th>
<th>Good</th>
<th>Intermediate</th>
<th>Poor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Years of survival if NGF</td>
<td>2.57</td>
<td>2.57</td>
<td>2.57</td>
</tr>
<tr>
<td>Years of survival if GF</td>
<td>3.38</td>
<td>1.50</td>
<td>0.91</td>
</tr>
<tr>
<td>QALYs if NGF</td>
<td>1.45</td>
<td>1.45</td>
<td>1.45</td>
</tr>
<tr>
<td>QALYs if GF</td>
<td>1.94</td>
<td>0.81</td>
<td>0.46</td>
</tr>
</tbody>
</table>

Note: GF = growth factor, NGF = non-growth factor. QALY = Quality-adjusted life years.
Assumes a 30% response rate to NGF therapy in a 60-year-old.


So ESAs Are Safe, Right???

AMGEN

IMPORTANT DRUG WARNING

SUBJECT: Additional data showing increased mortality and Tumor
Progression with EPOGEN® (EPOGEN®) and Aranesp®
March 7, 2008

Dear Healthcare Professionals

Recent data have emerged from several randomized clinical trials with EPOGEN® and Aranesp® showing increased mortality and tumor progression in certain high-risk patient populations. These findings are based on new data from five randomized trials involving over 12,000 patients with cancer who received one of these agents for anemia management.

For patients with cancer who require anemia management, the American Society of Clinical Oncology (ASCO) guidelines recommend the use of ESAs (Erythropoietin-stimulating agents) only when transfusion support is not necessary at a hemoglobin level of 12 g/dL.

So ESAs Are Safe, Right???

<table>
<thead>
<tr>
<th>Study</th>
<th>Target</th>
<th>Achieved</th>
<th>Endpoint</th>
<th>Apheresis Protocol</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemo</td>
<td>Weekly</td>
<td>12, 14 g/dL</td>
<td>12, 14 g/dL</td>
<td>12, 14 g/dL</td>
<td>Decreased OS in lower survival</td>
</tr>
<tr>
<td>C. Study 5</td>
<td>RBC transfusion (n=4)</td>
<td>11.9 g/dL, 9.9 - 12.1 g/dL</td>
<td>Proportion of patients achieving a hemoglobin response</td>
<td>Decreased overall survival</td>
<td></td>
</tr>
<tr>
<td>C. Group 9</td>
<td>Safe Bosostat (n=36)</td>
<td>12.5 - 13 g/dL, 12.5 - 13 g/dL</td>
<td>Reduced transfusion burden</td>
<td>Decreased in hospital and surgical survival</td>
<td></td>
</tr>
</tbody>
</table>

So ESAs Are Safe, Right???

<table>
<thead>
<tr>
<th>Study</th>
<th>Target</th>
<th>Achieved</th>
<th>Endpoint</th>
<th>Apheresis Protocol</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemo Study 4</td>
<td>Cancer (n=112)</td>
<td>12.9 g/dL, 12.0 - 13.9 g/dL</td>
<td>Proportion of patients achieving a hemoglobin response</td>
<td>Decreased OS in lower survival</td>
<td></td>
</tr>
<tr>
<td>Non-Chemo</td>
<td>RBC transfusion (n=163)</td>
<td>12.5 g/dL, 12.0 g/dL</td>
<td>Not available</td>
<td>Decreased OS in lower survival</td>
<td></td>
</tr>
<tr>
<td>Chemo Study 5</td>
<td>RBC transfusion (n=112)</td>
<td>12.5 g/dL, 12.0 g/dL</td>
<td>Not available</td>
<td>Decreased OS in lower survival</td>
<td></td>
</tr>
<tr>
<td>Chemo Study 6</td>
<td>Non-Chemo (n=112)</td>
<td>12.5 g/dL</td>
<td>Not available</td>
<td>Decreased OS in lower survival</td>
<td></td>
</tr>
</tbody>
</table>

Did Anybody See a Study in Patients with BMF Disorders?
How Many MDS Patients Require Transfusions?


Phase I/II Study of Romiplostim

Dose Escalation Phase completed

Treatment Extension Phase ongoing

Option to continue romiplostim SC weekly after Week 4.
Intra-patient dose escalation allowed.
Data as of May 18, 2007

Romiplostim Platelet Response Rates: Patients on Treatment Extension

<table>
<thead>
<tr>
<th>Category</th>
<th>N</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HI-P</td>
<td>35</td>
<td>19 (54)</td>
</tr>
<tr>
<td>Baseline platelet count</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 20 x 10^9/L</td>
<td>11</td>
<td>6 (55)</td>
</tr>
<tr>
<td>≥ 20 x 10^9/L</td>
<td>24</td>
<td>13 (54)</td>
</tr>
<tr>
<td>For pts achieving HI-P, plt count &gt; 100x10^9/L for ≥ 8 consecutive wks, n (%)</td>
<td>19</td>
<td>12 (63)</td>
</tr>
</tbody>
</table>

What About Neutropenia?

It is NOT routinely recommended that MDS patients with disease-related neutropenia receive antibiotic prophylaxis.

Patients with therapy-related neutropenia do receive antibiotic prophylaxis.

These recommendations are not evidence-based.

Conclusions (I)

• ESAs are used widely in MDS
• They work in approximately 40% of people
• We have ways of determining in whom they will work best
• They may provide a survival advantage compared to NGF or transfusions
• In solid cancer patients, they should be used judiciously

Conclusions (II)

• Platelet GF are available, but not yet approved for use in MDS
• G-CSF/GM-CSF may be used with ESAs, rarely to boost the white blood cell count alone.
Thanks!

Cleveland Clinic Leukemia Program

Jaroslaw Maciejewski, MD, PhD
Yogen Saunthararajah, MD
Anjali Advani, MD
Matt Kalaycio, MD
Ed Copelan, MD
Ronald Sobecks, MD
Manuel Alfalle, MD
Ricki Englehardt, RN
Kristy Grimes, RN
Barb Tripp, RN, NP
Tina Piks, RN
Josephine Chan, PhD
April Smith, BA
Katarina Pautic, BA
Randy Davis, BA
Stephani Day, MS

And Our Patients!