Treatment goals in MDS

- Get rid of it
- If you can’t do that, make life better and longer
  - Improve blood counts
  - Improve quality of life
  - Decrease time to progression/leukemia

Hematopoietic Growth Factors: What are they?

- Synthetic versions of proteins normally made in the body to stimulate growth of red cells, white cells and platelets
- Promote growth and differentiation
- Inhibitors of apoptosis (cell death)

Erythropoietin (epo) in MDS

- Anemia is present in >80% of MDS pts at dx
- Transfusions help, but many issues
- Recombinant EPO is FDA-approved for treating anemia associated with kidney failure
- Has been used since about 1990 in MDS
- Response rates in about 15-30% of patients
- Many different studies including >1000 patients
- Part of the NCCN MDS treatment guidelines

- Often high endogenous epo levels
- Many different doses and schedules
- Higher response rates with epo + G-CSF if epo ≤500 mU/mL and transfusions <2 U/month
- Poor probability of response if epo >500 mU/mL and transfusions >2 U/month

Erythropoietin (epo) in MDS

- Varying response criteria in clinical trials: usually complete response is increase in hgb to at least 11.5 without transfusions, partial response increase of hgb by at least 1.5 g/dl or reduction in transfusion requirements
- Responses usually in 12-16 weeks
- Generally well-tolerated
- Side effects: hypertension, fever, headache, nausea, chest pain

Problem

- Studies of EPO in solid tumor patients showed increased heart attacks, stroke, heart failure, blood clots, increased tumor growth, death, especially when hgb > 12
- Has resulted in concern for MDS patients, but NO DATA yet showing these effects in MDS patients
- Has had major effects on insurance coverage

EPO in MDS: Good or Bad?

- Will be difficult to do a study in MDS proving EPO is safe, so concern will remain
- Note: JCO study, Jadersten et al (vol 26, July 2008): Erythropoietin and granulocyte-colony stimulating factor treatment associated with improved survival in MDS
- Mostly low-risk patients
- Erythroid response 39%, median duration 23 mos
- Improved survival in pts requiring fewer than 2 units/month
- No increased AML

Stimulating White Blood Cells

- Don’t treat the number, treat the patient
- Not for routine treatment
- Active infections, recurrent/resistant infections, neutropenic fever
- Can be combined with red cell growth factors to improve responses in some patients
- Side effects: fever, bone pain, injection site reactions
- Does stimulating white cells cause leukemia??

Romiplostim in MDS Summary

- In patients receiving azacitidine, romiplostim vs placebo:
  - increased PLT counts over time and increased PLT count nadir during treatment cycles
  - reduced incidence of clinically significant thrombocytopenic events
  - reduced incidence of PLT transfusions
  - fewer Grade ≥ 3 bleeding events
- Romiplostim plus azacitidine well-tolerated
Lenalidomide: Erythroid Response Data

<table>
<thead>
<tr>
<th>Data Parameter</th>
<th>Del 5q (n=148)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythroid response Transfusion indep</td>
<td>99 (67%)*</td>
</tr>
<tr>
<td>Minor (&gt;50% ↓)</td>
<td>13 (9%)</td>
</tr>
<tr>
<td>Median duration of transfusion independence †</td>
<td>&gt;104 wks</td>
</tr>
<tr>
<td>Median Hgb rise</td>
<td>5.4 g/dL (1.1–11.4)</td>
</tr>
<tr>
<td>Median time to initial response</td>
<td>4.6 wk (1–49)</td>
</tr>
</tbody>
</table>

*P<0.001; †not reached at median follow-up of 104 wk

90% of responses occur within the first 3 months

Practical issues with lenalidomide

- CBC weekly for at least first 8 weeks, significant neutropenia and thrombocytopenia
- Dose adjustments may be necessary for thrombocytopenia and neutropenia, but they may be indicative of response, especially in 5q- patients

Epigenetic Therapy

- Fully methylated DNA
- Hypomethylated DNA
- Unmethylated DNA
- Differentiation - Apoptosis - Senescence - Enhanced Immune Response

CALGB 9221 Phase 3 Trial of Subcutaneous Azacitidine vs Supportive Care

- RX RAEB
- RAEB-T
- CML (n=191)
- Supportive Care
- Azacitidine 75 mg/m2/day for 7 days every 28 days
- Response*: Continue No response*: Off study

Randomized Study of Azacitidine in Patients With MDS: Results

- (N=191)
- Azacitidine
- Supportive Care

Effect of Azacitidine on Quality of Life and Transfusions

Improvement in:
- Fatigue
- Dyspnea
- Physical functioning
- Positive affect
- Psychologic distress

45% became transfusion-independent
9% had a 50% reduction in transfusions


Azacitidine vs Supportive Care: Most Frequent Adverse Events (>30%)

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Azacitidine (n=220), %</th>
<th>Supportive care (n=92), %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>70.5</td>
<td>17.4</td>
</tr>
<tr>
<td>Anemia</td>
<td>69.5</td>
<td>64.1</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>65.5</td>
<td>45.7</td>
</tr>
<tr>
<td>Vomiting</td>
<td>54.1</td>
<td>5.4</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>51.8</td>
<td>30.4</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>48.2</td>
<td>29.3</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>36.4</td>
<td>14.1</td>
</tr>
<tr>
<td>Fatigue</td>
<td>36.9</td>
<td>35</td>
</tr>
<tr>
<td>Injection site erythema</td>
<td>35.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Constipation</td>
<td>33.6</td>
<td>6.5</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>32.3</td>
<td>10.9</td>
</tr>
<tr>
<td>Ecthymosis</td>
<td>30.5</td>
<td>15.2</td>
</tr>
</tbody>
</table>


Azacitidine Treatment Prolongs Overall Survival in Higher-Risk MDS Patients Compared with Conventional Care Regimens: Results of the AZA-001 Phase III Study

P Fenaux, MD, GJ Multi, MD, V Santini, MD, C Finelli, MD, A Gla goundidas, MD, R Schich, MD, A List, MD, S Gore, MD, J Sey neur, MD, E Hallelom-Lindberg, MD, J Bennett, MD, J Byrd, MD, J Backstrom, MD, L Zimmerman, BSN, D McKenzie, MS, CL Beach, PharmD and L Silverman, MD, on behalf of the International Vidaza High-Risk MDS Survival Study Group

Azacitidine vs. conventional care regimens

Lancet Oncology 2009;10(3)

Important features of this trial

- 79 sites in 15 countries
- Median age 69 years (38-88)
- 113 pts (32%) met WHO criteria for AML
- 18 pts with IPSS Int-1
- 8 patients sent for allo transplant (did not affect overall survival)
- Azacitidine given for median 9 cycles
Secondary endpoints also favored aza

- OS better for AZA in all cytogenetic subgroups, esp -7/del7q
- Time to AML 17.8 mos AZA, 11.5 mos CCR, p<0.0001
- Improved RBC Transfusion Independence with AZA – 45% with AZA vs 11% with CCR, p<0.0001
- Infections Requiring IV Antimicrobials – Reduced by 33% with AZA vs CCR

Further analysis of AZA-001

- AZA better survival and better tolerated than LDAC (Fenaux, Br J Hematol 2010)
- Older pts with 20-30% blasts improved OS with AZA (Fenaux, JCO 2010)
- Ongoing treatment with AZA beyond time of first response improved quality of response (Silverman, Cancer 2011)

Decitabine in MDS

- Nucleoside analogue (5-aza-2’-deoxycytidine)
- FDA approved on 5/2/06 for:
  - Previously treated and untreated MDS
  - De novo and secondary MDS
  - All FAB subtypes
  - IPSS Int-1, Int-2, and high-risk groups

Phase III Study of Decitabine in Myelodysplastic Syndrome

- Open-label, 1:1 randomized, multi-center study in the US and Canada
- Eligible Patients (N = 170)
  - Decitabine + Supportive Care*
    - 89 pts
  - Supportive Care
    - 81 pts
- Stratification
  - IPSS Classification
  - Prior Chemotherapy
  - Study Center
- Schedule: 15 mg/m² IV 3 hour infusion q 8 hrs x 3 days
- Kantarjian et al, Cancer. 2006 Apr 15;106(8):1794-803

- Complete remission 9%
- Cytogenetic remission 35% vs.10%
- Hematologic improvement 13% vs. 7%
- Overall improvement 30% vs. 7%
- Trend toward longer time to AML/death

Optimizing treatment with hypomethylating agents

• Can we predict who will respond?
• How do we select which one for which patient?
• Combinations?
• Can we predict resistance?
• Can we predict who should get ongoing cycles and who should stop?

Allogeneic Stem Cell Transplantation

• The only potentially curative treatment
• Almost always recommended for high-risk MDS patients <60 years
• Can definitely be done for patients >60 years
• Recent data suggest survival benefit for patients 60-70 years, but still controversial

Supportive Care

• Anti-microbial agents
• Blood transfusions
• ? Iron chelation

Excess Iron is deposited in multiple organs, resulting in organ damage

Iron overload
Capacity of serum transferrin to bind iron is exceeded

NTBI circulates in the plasma; Labile forms of NTBI (e.g. SPI enter cells and raise the levels of labile cell iron (LCI)

Excess iron promotes the generation of free hydroxyl radicals, propagation of oxygen-related tissue damage

Insoluble iron complexes are deposited in body tissues and end-organ toxicity occurs

Cardiac failure
Liver cirrhosis/ fibrosis/cancer
Diabetes mellitus
Infertility
Infectious osteonecrosis of the jaw

Chelation aims:

preventing LIP formation & LCI accumulation

Ok, so how do we know if there’s too much iron?
Assessing Iron Overload

• Serum ferritin concentration
  – Used in clinical practice globally
• Liver biopsy
  – Gold standard for kids, not feasible in most MDS
• Magnetic resonance imaging (MRI)
  – Investigational, potential for broad access
  – T2* cardiac MRI
• Magnetic susceptometry (SQUID)
  – Investigational, very limited access

Complications of iron overload: keep in mind…

• Most of the data are from children with thalassemia: severe anemia, chronic transfusions starting at age 1
• Iron-related heart disease most common cause of death
• Clear evidence that chelation with deferoxamine improved survival and helped liver and endocrine complications

Deferoxamine (Desferal®)

• Most clinical experience, dosing and administration well-known
• Reduces morbidity and mortality for sure in kids with thal, less clear in adults

Challenges of therapy

– Subcutaneous or IV administration
– Continuous 12-hour infusion 5–7 days/week rec’d
– Infusion-site reactions and pain
– Eye and ear side effects, need periodic exams
– Infectious complications
– High degree of noncompliance

• Survival correlated with compliance

The $6 billion question

• Does this mean iron overload is bad for everyone and chelation (treatment to get rid of iron) is good for everyone at risk of iron overload?

BUT…

• Limited evidence showing that iron causes clinically significant organ damage in MDS patients
• Unclear how to measure iron overload (ferritin, transferrin saturation, NTBI, liver biopsy, SQUID, liver MRI, cardiac T2* MRI)
• No prospective data demonstrating that chelation improves survival
• Unclear which chelator to use (deferoxamine, deferiprone, deferasirox) and how to measure efficacy

Critical questions…

• Does iron overload shorten survival in MDS? Maybe
• Does iron overload hasten transformation to leukemia? Maybe
• Does iron overload worsen hematopoiesis? Maybe
• Does iron overload worsen outcomes of stem cell transplantation by increasing infections and/or VOD? Probably
• Does chelation treatment get rid of excess iron? Seems to
So, now what do I do? Consider...

- Transfusion-dependent patients with IPSS low or int-1 MDS (or WHO RA, RARS, 5q-syndrome)
- Life expectancy > 1 year
- Serum ferritin > 1000 μg/L or evidence of iron-related organ damage; target serum ferritin < 1000
- Higher risk MDS patients who are candidates for stem cell transplant
- Deferoxamine or deferasirox with close clinical and lab monitoring
- Don’t just use deferoxamine at times of transfusion

Conclusions

- Treatment options for MDS better than 10 years ago, but much work still needed
- Interesting new drugs, but no magic bullet yet
- Features of personalized medicine starting to take shape
- Need to optimize stem cell transplantation
- CLINICAL TRIALS

Selected Trials at Weill Cornell - NYP

- Vosaroxin for patients previously treated with aza or dac
- SGI-110 for patients previously treated with aza or dac
- Rigosertib for patients previously treated with aza or dac
- Azacitidine + pracinostat/placebo for patients with untreated int-2 or high-risk MDS

Reassurance with Personalization

- We will get to know everything about you
- Your medical issues
- Your family
- Your pets
- Your hobbies
- YOU as a person

Proposed treatment algorithm for patients with MDS

Low-risk (IPSS low, INT-1) (BM blasts < 10%)

- Iron chelation
- Growth factors (Epo, G-CSF)
- MTI (5-AZA/decitabine)
- Lenalidomide (5q-)
- Immunomodulation
- Clinical trial

High-risk (IPSS INT-2, high) (BM blasts > 10%)

- Intensive chemotherapy
- MTI (5-AZA/decitabine)
- Clinical trial

Failure/Progression

Allo SCT

Any age

Age ≤ 60

Age ≥ 60

Failure

Failure

Consider in younger patients with diploid cytogenetics
Consider earlier in younger patients

Atallah. Cancer Inv. 2008;26:208-16
But, can we cure with personalization?

- Using advanced technologies to identify specific characteristics of an individual’s cancer cells
- Mutations
- Signaling pathways
- A unique ‘fingerprint’
- Then, just find the right drug, right?

We need personalized medicine, not anecdotal medicine

- One patient per regimen doesn’t work
- Start with a treatment backbone, then tailor
- Novel and efficient clinical trial designs
- Novel drug development strategies
- Clinical trials for newly diagnosed and relapsed patients AND for those in remission
- Study the cured patients: why are some cured, while others are not?

IMPORTANT CHANGES

- New, broad consent forms for diagnostic material: don’t throw science in the garbage (literally!)
- Expanded biobanking with clinical annotation
- Change the culture: none of this will work if patients don’t participate

CRUSHMDS.ORG
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I’d be happy to see you at Weill Cornell/NYP!

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