Welcome to
Master Class for Oncologists

New York, NY
October 24, 2008

Session 1:
1:00 PM - 1:45 PM
Acute Leukemia and Myelodysplasia
Speaker:
Richard M. Stone, MD

Presenter Disclosure Information

The following relationships exist related to this presentation:

• Dr Richard M. Stone has served as a consultant for Genzyme and Eisai and is on the speaker’s bureau for Celgene and Bristol-Myers Squibb.

Off Label/Investigational Discussion
In accordance with Pri-Med Institute policy, faculty have been asked to disclose discussion of unlabeled or unapproved use(s) of drugs or devices during the course of their presentations.

Acute Leukemia and Myelodysplastic Syndrome: Treatment

• AML: RISK ADJUSTED TREATMENT
• APL: CURATIVE TREATMENT OPTIONS
• ALL: RISK-ADAPTED TREATMENT
• MDS: ALGORITHM

Audience Response Question: 45 YO M w AML

• M2 AML w normal cytogenetics
• NPM1 mutation and FLT3 ITD WT
• Achieves CR with standard rx

Most appropriate consolidation?

1. None needed
2. Sib allo
3. High-dose chemo w autol PBSC rescue
4. High-dose ara-C

AML: RISK ADJUSTED TREATMENT

Need to know

• PATIENT AGE
• CYTOGENETICS
• Molecular studies
  – FLT3 ITD
  – NPM1 mutation
Older Patients with AML: Inferior Outcomes

<table>
<thead>
<tr>
<th>Age</th>
<th>Complete Remission Rate</th>
<th>Disease-free Survival Rate</th>
<th>Early Death (%)</th>
<th>Overall % Survival (median)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;60</td>
<td>70%</td>
<td>45%</td>
<td>10%</td>
<td>30% (24 mo)</td>
</tr>
<tr>
<td>&gt;60</td>
<td>45%</td>
<td>20%</td>
<td>25%</td>
<td>10% (10 mo)</td>
</tr>
</tbody>
</table>

*Based on CALGB, MRC trials in which adults of all ages were eligible*

Inferior Outcome in Older Patients with AML: Reasons

- Decreased host tolerance
  - Impaired stem cell reserve
  - Co-morbid diseases
  - Decreased chemotherapy clearance
- Intrinsically increased disease resistance
  - Ratio of favorable (eg, t(8;21))/unfavorable (eg, −7) cytogenetics is low
  - High expression of drug resistance proteins
  - Higher incidence of antecedent heme disorders

Relationship between Karyotype and Prognosis in AML

<table>
<thead>
<tr>
<th>Karyotypic Abnormality</th>
<th>5 yr Survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>45</td>
</tr>
<tr>
<td>t (15; 17)</td>
<td>65</td>
</tr>
<tr>
<td>t (8; 21)</td>
<td>65</td>
</tr>
<tr>
<td>inv 16</td>
<td>65</td>
</tr>
<tr>
<td>trisomy 8</td>
<td>45</td>
</tr>
<tr>
<td>11q23</td>
<td>45</td>
</tr>
<tr>
<td>trisomy 21</td>
<td>45</td>
</tr>
<tr>
<td>-7</td>
<td>10-15</td>
</tr>
<tr>
<td>5q(-)</td>
<td>10-15</td>
</tr>
<tr>
<td>complex (&gt;3)</td>
<td>10-15</td>
</tr>
</tbody>
</table>


Note: All 1966 patients in Grimwade’s analysis and 251/285 in Bloomfield’s report were under 60.

DFS and OS According to the combined NPM1 and FLT3-ITD Status

<table>
<thead>
<tr>
<th>Karyotypic Abnormality</th>
<th>5 yr Survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NPM1-FLT3-ITD+</td>
<td>45</td>
</tr>
<tr>
<td>NPM1-FLT3-ITD-</td>
<td>65</td>
</tr>
<tr>
<td>NPM1+FLT3-ITD+</td>
<td>65</td>
</tr>
<tr>
<td>NPM1+FLT3-ITD-</td>
<td>65</td>
</tr>
<tr>
<td>NPM1+FLT3-ITD-</td>
<td>65</td>
</tr>
</tbody>
</table>

AML: Treatment of those under age 60 (non-APL)

**Induction**
- anthracycline (3d) plus cytarabine (7d, IVCI)

**Post-remission Therapy**
- intensive chemo
- auto BMT
- allo BMT

AML: Induction

- 3d of idarubicin (12 mg/m² qd) or daunorubicin (45 mg/m² qd) better than doxorubicin
- Add 6-thioguanine (common in UK)? no clear benefit
- Add etoposide? DFS benefit, no survival benefit
- Add high-dose ara-C? original reports of 90% CR rate not confirmed
- Substitute high-dose ara-C? DFS benefit, no survival benefit
Post-Remission High-Dose ara-C

- ECOG trial: one cycle of high-dose ara-C (DFS= 27%) superior to lower-dose therapy
- CALGB trial (4 cycles of high-dose ara-C plus maint.) superior to lower-dose ara-C and grossly equivalent to BMT results (3 year DFS= 44%)

CALGB: DFS Benefit Only in Pts <60 years receiving High-Dose ara-C

- Patients in Remission (%)
  - Age <60: 3 g/m² = 156, 400 mg/m² = 156, 100 mg/m² = 155, p = 0.0007
  - Age >60: 3 g/m² = 31, 400 mg/m² = 50, 100 mg/m² = 48, p = 0.22

CALGB 8525: Survival Benefit in Pts <60 years old Receiving High-Dose ara-C

- Patients alive (%)
  - Months after Randomization: 3 g/m² = 156, 400 mg/m² = 156, 100 mg/m² = 156

CALGB 8525: Survival Benefit in Pts <60 years old Receiving High-Dose ara-C

- Survival Benefit in pts <60 receiving High-Dose ara-C
  - CBF n=57, NL n=140, other n=88
  - 3yr DFS:
    - CALGB 8525: Survival Benefit in pts <60 receiving High-Dose ara-C

ALLOTX in CR1?

- Prospective trials assigning those w matched sib donors to allotx and others randomized to chemo ‘v’ autotx
  - Autotx=chemo
  - Allo (low relapse rate) ‘v’ auto/chemo (low TRM) equivocal (depends on timing, intensity of chemo, allotx TRM)

- Recent studies suggest that MUD allo=sib donor allo

- Bottom line: the younger the pt or the higher the risk (2 ind’n, non-fav chromo, adverse genetics) the more appropriate is allotx, even MUD allotx for highest risk

AML RX pts< age 60: Guidelines

- Standard induction chemo: 3+7
- Post-remission therapy
  - if sib allo
    - BMT if poor cytogenetics
    - High-dose ara-C in favorable cytogenetics
    - allo BMT ‘v’ APSCT ‘v’ high-dose ara-C in intermediate cytogenetics
  - if unrelated donor
    - BMT if definitively poor cytogenetics
AML: Treatment of those over age 60

- Induction
  - as in younger adults, 3d of an anthracycline and 7d of cytarabine is the standard (CR rate=45%)
- Post-remission chemotherapy
  - Leads to long-term DFS in less than 20%
  - intensive approaches not useful
- Newer therapies needed

Induction Chemotherapy in Older Patients with AML

- Standard: daunorubicin 45-60 mg/m²/d x 3d + cytosine arabinoside 100-200 mg/m²/d by continuous infusion for 7d
- Idarubicin or mitoxantrone not better than dauno
- Add etoposide or increase dauno dose: possible, but clearly better
- Ongoing trials are determining if ‘tolerable’ single agent rx (eg, clofarabine, decitabine, cloretazine) might= 3+7
  - Especially in those destined to do very poorly w 3+7
  - Age > 70
  - PS=2 +/- co-morbid ds
  - Adverse cytogenetics

AML in > 60 yo: Lack of Effect of induction chemo choice on DFS- HOVON AML-9

Post-remission Therapy in Older Patients with AML

### CALGB 8525

<table>
<thead>
<tr>
<th>Cytosine arabinoside*</th>
<th>5-y Disease-free survival</th>
<th>Overall survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>100 mg/m²/d on d 1-5 x 4</td>
<td>≤ 14%</td>
<td>8%</td>
</tr>
<tr>
<td>400 mg/m²/d on d 1-5 x 4</td>
<td>≤ 14%</td>
<td>8%</td>
</tr>
<tr>
<td>3mg/m²/h q12h on d 1,3,5 x 4</td>
<td>≤ 14%</td>
<td>8%</td>
</tr>
</tbody>
</table>

*Followed by 4 cycles daunorubicin x 1 day + cytosine arabinoside x 5 days

### CALGB 8923

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Disease-free survival</th>
<th>Overall survival</th>
<th>5-y Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytosine arabinoside 100 mg/m²/day x 5 days IV/Ci x 4</td>
<td>10 mos</td>
<td>18 mos</td>
<td>13%</td>
</tr>
<tr>
<td>Cytosine arabinoside 500 mg/m² + mitoxantrone 5 mg/m² q12h x 6 doses x 2</td>
<td>9 mos</td>
<td>15 mos</td>
<td>19%</td>
</tr>
</tbody>
</table>

### EORTC/HOVON

| Cytosine arabinoside 10 mg/m² SC q12h x 12days q 6 weeks x 8 | 20% | 79 wks |
| Observation | 7% | 62 wks |
### Therapy in Older Patients with AML: Conclusions

- **CLINICAL TRIAL PREFERRED**
  - Esp if v high risk features (eg, age >70, PS=2, adverse cytogenetics, co-morbid ds)

- Daunorubicin (45 mg/m² on days 1-3) + cytosine arabinoside (200 mg/m² on days 1-7) (“3+7”) remains the standard

- Repeat (actual or modified) induction, low- or moderate-dose cytosine arabinoside (100-400 mg/m² × 5 d) in the post-remission setting

- Consider consolidation with RIC allo on trial

### Audience Response Question: 45 YO M w AML

- M2 AML w normal cytogenetics
- NPM1 mutation and FLT3 ITD WT
- Achieves CR with standard rx

**Most appropriate consolidation?**

1. None needed
2. Sib allo
3. High-dose chemo w autol PBSC rescue
4. High-dose ara-C

### Audience Response Question: 35 Y/O F w APML?

- t (15;17)
- WBC=3K, plt=11K
- Achieves CR with ATRA/3+7 (PML-RARα still detectable)

**What consolidation therapy?**

1. High-dose ara-C
2. Ida/ATRA
3. Arsenic trioxide
4. AlloTx (pt has a matched sib)

### Treatment of acute promyelocytic leukemia

#### NEED TO KNOW

- Document disease
  - Cytogenetics or FISH for t(15;17) (variants rare, but are unresponsive to ATRA) AND/OR
  - RT-PCR for PML-RARα

- Risk assessment
  - WBC >10K= high risk
  - WBC <10K, plt >40K= low risk

- Is pt an anthracycline candidate

### Treatment of acute promyelocytic leukemia

#### Disease Features

- low WBC, DIC, CD33+, HLA-DR-
- DIC (dLt. procoag granules, +/- activation of fibrinolysis) responds to ATRA
- t(15;17) and/or PML-RARα by RT PCR req. for dx
- secondary cases occur, they fare well

60-80% DFS with current therapy

- Emerging concern re late MDS, CNS relapse

- Induction
  - ATRA alone leads to non-durable CRs via diff.
  - anthracycline (dauno or ida) x 3-4d (+/-) cytarabine plus ATRA (until CR) is best

- Post-remission chemotherapy with anthracycline +/- cytarabine +/- ATRA (emerging data: use hidac in high risk)

- Maintenance chemo with ATRA +/- oral antimetabolites (6-MP plus MTX)
SPANISH PETHEMA RESULTS

- IDA+ ATRA induction
- 3 cycles consolidation (anthracycline only +/- ATRA)
- 1 year of ATRA/antimetabolite rx maintenance
- N=384
  - 90% CR rate
  - 7.5% relapse rate (21 month f/u) if ATRA in consolidation
  - Best px: WBC<10; plt >40.


US Multicenter Trial of Arsenic Trioxide in Relapsed APML

- As₂O₃ 0.15 mg/kg over 1-2h qd until CR
  - 25d consolidation cycle
- n=40, heavily pretreated
- 85% CR rate (failure 3 resistant, 3 deaths)
- median time to CR=59 d
- 86% of CR pts achieved PCR negative status after 1 or 2 cycles
- Most common AEs: hypokalemia, hyperglycemia, neutropenia; nausea, neuropathy, and headache also noted; QT prolongation in 16 wo. clinical effects; “retinoic acid syndrome” in 10.


APL Intergroup Study: Role of Arsenic Trioxide in First CR

- APL confirmed by RT-PCR
- ATRA (d1 to CR) dauno (d3-6) ara-C (d3-9)
- CR patients are randomized to receive:
  - As₂O₃ 0.15 mg/kg/d IV x 25d x 2 cycles plus dauno/ATRA x 2
  - dauno/ATRA x 2 alone
- 2nd randomization to:
  - ATRA 45mg/m²po x 7d every other week x 1 yr
  - ATRA 45mg/m²po x 7d every other week plus MTX/6-MP x 1 yr

ASCO 2007- Arsenic : better DFS and OS

CALGB 9710: DFS By RX and WBC

- p = 0.0016, HR 2.24

PETHEMA LPA 99 trial (no As₂O₃) Event-free survival

- 96% Low risk
- 86% Intermediate
- 59% High risk

n = 564

ATRA+As₂O₃ in Untreated APL.
Treatment Design and Monitoring

Induction
- ATRA 45 mg/m²d P.O. until CR
- As₂O₃ 0.15 mg/kg/d I.V. D10 until CR
- Gemtuzumab ozogamicin (GO) 9 mg/m² D1, if WBC>10x10⁹/L

Maintenance
- As₂O₃ 0.15 mg/kg I.V. 5d/ek x 4 wks
  - 1 month on, 1 month off x 3; total doses, 60
- ATRA 50 mg/m²d P.O.
  - 2 wks on, 2 wks off x 6 months
- Total duration, 6 months

BM PCR q 3 mos. If (+) → repeat in 2 wks → if (+) → GO
ATRA+As2O3 in Untreated APL. Outcomes by Age

Survival

Relapse-Free Survival of CRs

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  - Arsenic trioxide
  - AlloTx (pt has a matched sib)

Audience Response Question: 71 YO M w ALL?

- Pre-B cell ALL
- WBC=100K, plt=41K at dx
- Has hypertension, DM, mild CHF

What induction therapy is most appropriate for this patient?
1. 5 drug induction f/b imatinib
2. 5 drug induction plus imatinib
3. Imatinib
4. Dasatinib plus steroids

ALL

Need to know

- AGE
- CYTOGENETICS
  - Philadelphia chromosome (more common in older)
  - t(4;11), and (8;14)- unfavorable
- IMMUNOPHENOTYPE
  - T v pre-B

ALL: Therapy

- Childhood ALL-85% cured: The great success story based on anthracycline, vincristine, steroid, L-asp induction; CNS prophylaxis; intensification; and POMP maintenance
- Adult ALL-35% cured: More difficult biology (increased inc PH+), but perhaps therapy could be improved even with available agents
  - Ongoing trial lead by DFCI adult leukemia team: almost exact pediatric rx to adults
ALL: Treatment in Adults

- Largely based on high-risk children
  - Obligate requirement for BMT in PH+
    - French prospective trial suggested no benefit for high-dose therapy in any other subgroup
  - CALGB phase II trials: CTX/dauno/VCR/L-asp/pred ind’n, early intens, CNS prophylaxis, late intens, maint: 40% DFS
- Equivalent results with
  - Hyper CVAD (MD Anderson)
  - ara-C plus high-dose mitoxantrone (MSKCC)

ALL in older adults

- Rare ds, but as for AML, results highly inferior c/w younger adults
  - CR=50%, DFS=10-20%
  - Based on dose-reduced standard CALGB-Larson regimen
    - CTX 800mg/m² d1, dauno 30 mg/m² d1-3, prednisoone
    - 60 mg/m² d1-7, VCR 2 mg d 1,8,15,22 and L-asp 6000 U/m² 2x/week
    - G-SCF on d4 till ANC recovery is beneficial (CALGB 9011)
- Intrinsic Biologic Hurdle= High incidence of PH + ds in this age cohort

PH+ ALL: Single agent bcr-abl inhibition

- Often considered together with CML-LBC
- 70% response (20% CR) rate with imatinib, but responses of brief duration
- ASH 2007: GIMEMA LAL1205- dasatinib monotherapy upfront in older adults with PH+ALL (n=23); median age=57
  - Steroids d →7 to 30 w dasatinib 70 mg po bid x 84d
    - CHR by d 22 in 100%
    - All but one in CCR but w only 4.5 month median f/u
    - No toxic deaths
    - qPCR markedly reduced in most pts by d 84

Outcome Comparison of Adolescent/Young Adults with ALL on Pediatric vs. Adult Clinical Trials

<table>
<thead>
<tr>
<th>Cooperative Group</th>
<th>Study Period/No. Pts.</th>
<th>Age (yrs)</th>
<th>CR (%)</th>
<th>DFS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>North America (Stock)</td>
<td>1988-1998/196 pts</td>
<td>16-21</td>
<td>96%</td>
<td>64%</td>
</tr>
<tr>
<td>CALGB (adults)</td>
<td>1993-1994/77 pts</td>
<td>15-20</td>
<td>94%</td>
<td>67%</td>
</tr>
<tr>
<td>Italian (Testi)</td>
<td>1985-1999/47 pts</td>
<td>15-21</td>
<td>94%</td>
<td>66%</td>
</tr>
<tr>
<td>Dutch (deBois)</td>
<td>1993-1994/73 pts</td>
<td>15-21</td>
<td>91%</td>
<td>31%</td>
</tr>
<tr>
<td>Italian (Testi)</td>
<td>1998-2000/153 pts</td>
<td>14-18</td>
<td>94%</td>
<td>63%</td>
</tr>
</tbody>
</table>

Combination of TKI plus chemo in Ph+ ALL: The New Standard

- Hyper CVAD plus imatinib (I given 400 mg given on day 1-14 of each course, f/b 12 mo of qd imatinib):
  - MDAnderson study begun in 2001
  - alloSCT in CR1 when feasible
- More recent modification using higher-dose imatinib for longer period n=54 (mainly new dx)
  - 93% CR rate
  - Comp molec CR=52%
  - N=16 had SCT, but this group did not do any better than no SCT pts
  - Much better results c/w hyperCVAD hist controls
    - 3 yr DFS of 66 ‘v’14%
    - Some relapsed with TKD mutations, suggesting role for newer TKIs

Audience Response Question: 71 YO M w ALL?

- Pre-B cell ALL
- WBC=100K, plt=41K at dx
- Has hypertension, DM, mild CHF

What induction therapy is most appropriate for this patient?

1. 5 drug induction f/b imatinib
2. 5 drug induction plus imatinib
3. Imatinib
4. Dasatinib plus steroids
?71 yo M w MDS

WBC=1.5K, plt=41K, HCT=26%, ANC=490

- BM: 12% blasts
- Cytogenetics: 5q-, 7-, others
- Best treatment?
  - 5-azacitidine
  - Decitabine
  - Lenalidomide
  - Lenalidomide plus 5-azacitidine

Audience Response Question: 71 yo M w MDS

- WBC=1.5K, plt=41K, HCT=26%, ANC=490
- BM: 12% blasts
- Cytogenetics: 5q-, 7-, others

Best treatment?
1. 5-azacitidine
2. Decitabine
3. Lenalidomide
4. Lenalidomide plus 5-azacitidine

MDS

Need to know

- Host Factors
  - Age
  - Co-morbid conditions, PS
- Disease Factors
  - Marrow Blasts
  - CBC
  - Cytogenetics
  - ?Needs transfusion

Myelodysplasia: General treatment principles

BMT:
The only known curative modality, but practical only in a small subset

Non-curative goals:
decreased transfusion, infection, increased quality of life

IPSS Risk Stratification

<table>
<thead>
<tr>
<th>Prognostic Grade</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>0</td>
</tr>
<tr>
<td>Int-1</td>
<td>0.5</td>
</tr>
<tr>
<td>Int-2</td>
<td>1.0</td>
</tr>
<tr>
<td>High</td>
<td>1.5</td>
</tr>
<tr>
<td>Very High</td>
<td>2.0</td>
</tr>
</tbody>
</table>

Marrow blasts [%]
- <5%
- 5-10%
- 11-20%
- 21-30%

Karyotype class
- Good
- Intermediate
- Poor

# of cytopenias
- 0 or 1
- 2 or 3

* Karyotypes: Good = normal, -Y, del(5q) alone, del(20q) alone; Poor = chromosome abnormalities in samples, intermediate = other karyotypes. ** Cytopenias: Hb < 10 g/dL, ANC <1800/uL, platelet <100,000/uL.


IPSS Predicts Overall Survival and AML Evolution In De Novo MDS

<table>
<thead>
<tr>
<th>Risk Groups</th>
<th>Low</th>
<th>Int-1</th>
<th>Int-2</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>IPSS</td>
<td>0</td>
<td>0.5-1.0</td>
<td>1.5-2.0</td>
<td>2.5-3.5</td>
</tr>
</tbody>
</table>

Death (n=16) AML
WHO Classification-Based Prognostic Scoring System (WPSS)

<table>
<thead>
<tr>
<th>Variable</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>WHO category</td>
<td>RA, RAR, 5q-</td>
<td>0q23, 0q24-RARS, RAEB-1</td>
<td>RAEB-2</td>
<td></td>
</tr>
<tr>
<td>Karyotype*</td>
<td>Good</td>
<td>Intermediate</td>
<td>Poor</td>
<td></td>
</tr>
<tr>
<td>Transfusion requirement</td>
<td>No</td>
<td>Regular</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Karyotype per IPSS classification
Transfusion: RBC q8 wks over 4 months

Allogeneic Marrow Transplantation in MDS

- "Only known curative modality"
- HLA-matched sibling donor
  - 4 yr: DFS- 40-50%, relapse- 25%
  - Best results: younger age, short dx-tx interval, RA/RARS
  - Late relapses rare
  - DLI salvages 25% relapses
- HLA-matched unrelated donor
  - 20-40% 2 yr DFS
  - Though severe GVHD reported, results may be improving with more detailed HLA typing

MDS: Role of Chemotherapy

- Induction chemo not indicated in MDS, especially now that MDS defined as <20% blasts
- Role of pre-BMT chemo for pts w. excess blasts?
  - Lower marrow blast count at time of tx generally better
  - Those who respond to pre-BMT chemo fare better than those who do not, suggesting that response to chemo may merely identify better prognosis patients
  - Probably more important in pts having RIC allo tx

AlloTX in MDS: Approximation of Life Expectancy (Years)

<table>
<thead>
<tr>
<th>Immediate Transplant</th>
<th>Transplant in 2 Years</th>
<th>Transplant at Progression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>6.51</td>
<td>6.86</td>
</tr>
<tr>
<td>Int-1</td>
<td>4.61</td>
<td>4.74</td>
</tr>
<tr>
<td>Int-2</td>
<td>4.93</td>
<td>3.21</td>
</tr>
<tr>
<td>High</td>
<td>3.20</td>
<td>2.75</td>
</tr>
</tbody>
</table>

GFs for anemia in MDS

- EPO alone
  - 20% response
  - perhaps higher if [EPO] < 100 mIU/ml, not tx-dep
  - RR: 8% in RARS, 21% in RA or RAEB
  - Best dose: > 50K/week
- G-CSF+ EPO
  - perhaps a 40% E-lineage response, with half losing it if G stopped
Growth Factors other than EPO in MDS

- G-CSF or GM-CSF
  - WBC increases in > 80%
  - No certain pro-leukemic effect
  - No survival prolongation (rand. trial w. G ‘v’ obs)

- Thrombopoietins:
  - IL-11: limited evaluation suggests little activity
  - Pegylated TPO (MGDF): no being developed
  - AMG531 (romiplostat,TPO-agonist) quite active in ITP, early trials in MDS ongoing

Iron Overload

- Common in patients with bone marrow failure receiving chronic transfusion support
- Important consequences for potential organ function and survival
- Iron burden should be monitored in patients with greater than 20-30 unit transfusion history
- Chelation can be effective, but it is NOT CLEAR whether chelation improves survival

Deferasirox Study: Reduction in Labile Plasma Iron

<table>
<thead>
<tr>
<th>Timepoint</th>
<th>Baseline</th>
<th>3 months</th>
<th>6 months</th>
<th>9 months</th>
<th>12 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Labile Plasma Iron (μmol/L)</td>
<td>Mean</td>
<td>Median</td>
<td>Mean</td>
<td>Median</td>
<td>Mean</td>
</tr>
<tr>
<td>n=131</td>
<td>0.35</td>
<td>0.20</td>
<td>0.30</td>
<td>0.15</td>
<td>0.25</td>
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<tr>
<td>n=109</td>
<td>0.40</td>
<td>0.25</td>
<td>0.35</td>
<td>0.20</td>
<td>0.40</td>
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<tr>
<td>n=76</td>
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<td>0.30</td>
<td>0.40</td>
<td>0.25</td>
<td>0.50</td>
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<tr>
<td>n=47</td>
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<td>0.35</td>
<td>0.45</td>
<td>0.30</td>
<td>0.55</td>
</tr>
<tr>
<td>n=34</td>
<td>0.55</td>
<td>0.40</td>
<td>0.50</td>
<td>0.40</td>
<td>0.60</td>
</tr>
</tbody>
</table>

Immunosuppression in MDS

- Theory that the pathophysiology of cytopenias in non-excess blast subtypes of MDS may be due to T-cell mediated suppression, as in aplastic anemia
- Immunosuppression in indolent subtypes of MDS, particularly hypoplastic refractory anemia with normal chromosomes
  - Cyclosporin A: 50% response rate (Czech)
  - Antithymocyte globulin: 50% RBC and/or platelet response (NCI, n=60)
  - Blast chance: younger pts and lower plt counts, HLA-DR15

Anti-apoptotic/anto-angiogenic therapy in MDS

- Amifostine, chemo/radio-protectant which promotes growth and survival of stem cells in vitro
  - lineage responses in 36%

- Thalidomide (n=81, most didn’t tol full course)
  - decreased transfusion req in 10 indolent pts

- Lenalidomide (10 mg po qd starting): 66% RBC tx-indep and 50% cytogenetic response in 5q- patients (Approved); 26% rate of RBC tx indep in non-5q- (not approved)
  - indolent histology (low and int-1, and preserved ANC and plt only)

Developing New Therapies in MDS: Differentiation

- No-gene-expression
- Blast
- Poly
- Gene-expression
- Differentiation agents
- narrow (thalidomide) groups to be studied
- broad (megadose) groups to be studied

Differentiation Therapy in MDS

- Overcome Block in Failure to produce mature cells
  - Low-dose ara-C: responses in 10-20%, rarely used now
  - ATRA: lack of benefit in randomized trial
- Promote transcription of differentiation-associated genes
  - histone deacetylase inhibitors (e.g., phenylbutyrate, depsipeptide, SAHA, MS275, LBH589) in development
  - DNA hypomethylating agents (5-azacytidine and decitabine)
    - The most active available category of agents in MDS (5-aza FDA approved 5-04; decitabine 6-06)

QOL QOL QOL

* Minimum duration of supportive care = 4 months
  unless transform to AML; death or plts ≤ 20 x 10^9/L at week 8 or later

CALGB 9221 A Randomized Phase III Controlled Trial of sc Azacitidine in Myelodysplastic Syndromes

1) Supportive Care*
2) Azacitidine 75mg/m^2 x 7 days q28 x 4

Exit Criteria

- No Response
- Continue until Endpoint

Response

- Continue Rx
- Off Study

Time to AML Transformation

Survival: FAB Classification

Azacitidine Survival Study

Survival Study Design

Patient Randomized into Study (higher risk)

Azacitidine 75 mg/m^2 x 7 days Every 28 days

Standard of Care Options consist of:
1. Best Supportive Care
2. Low-Dose Ara-C
3. Standard Chemotherapy

Results

- Median survival:
  - 24.4 mos for Azacitidine vs 15 mos for conventional care regimens (stratified log-rank p-value of 0.0001)
  - 9.4 months median survival benefit for patients on Vidaza compared to CCR
- Extends overall survival by 74%
  - HR =0.58 (95% CI: 0.43-0.77)
- Two-year survival rate:
  - 50.8% for Azacitidine vs 26.2% for CCR (p<0.0001)
  - Note: alternative dosing strategies and IV formulation may be equivalent
DECITABINE in MDS

Like 5-azacytidine, decitabine inhibits DNA methyltransferase; at low doses may cause differentiation

- Randomized trial of decitabine 15mg/m² over 4 h IV q8 h x 3d ‘v’ obs lead to approval of decitabine spring 06
- Delayed time to AML transformation in high risk pts.
- New schedule in common use: 20 mg/m²/d x5d

MDS: General Algorithm

- Consider alloBMT if poor px and under age 55-60 (45-55 for MUD donor)
  - Induction chemo pre-BMT or rx as AML
- Trial of EPO in selected pts ([EPO] < 500 mIU/ml)
- Lenalidomide in 5q-
- Clinical Trial if possible; if not
  - Consider ATG in hypoplastic
  - Consider 5-aza/decitabine in all others

Audience Response Question: 71 yo M w MDS

WBC=1.5K, plt=41K , HCT=26%, ANC=490

- BM: 12% blasts
- Cytogenetics: 5q-, 7-, others
- Best treatment?
  1. 5-azacitidine
  2. Decitabine
  3. Lenalidomide
  4. Lenalidomide plus 5-azacitidine

Acute Leukemia and MDS Treatment: Conclusion

- Good prognosis diseases
  - Childhood ALL and APL
    - Consider reducing therapy to reduce toxicity
- Poor prognosis diseases
  - ALL and AML in adults
    - Refining role of BMT, adjunctive agents to chemo
- Essentially incurable diseases
  - MDS and AML in older adults
    - New insights needed
Questions & Answers

?