Session 1:  
1:00 PM – 1:45 PM  

Recent Advances in Understanding and Treatment of Acute Leukemia and Myelodysplasia  
Speaker:  
Richard M. Stone, MD  

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  
- Has healthy matched sib  

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

Older Patients with AML: Inferior Outcomes  

<table>
<thead>
<tr>
<th>Age</th>
<th>Complete Remission</th>
<th>Disease-free Survival</th>
<th>Early death</th>
<th>Overall % Survival</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

Presenter Disclosure Information  
The following relationships exist related to this presentation:  
- Dr Stone serves as a consultant for Genzyme, Sunesis, and Eleos.

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.
Inferior Outcome in Older Patients with AML: Reasons

- Decreased host tolerance
  - Impaired stem cell reserve
  - Comorbid diseases
  - Decreased chemotherapy clearance

- Intrinsically increased disease resistance
  - Ratio of favorable (e.g., t(8;21))/unfavorable (e.g., -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>


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

AML: Treatment of Patients < 60 (non-APL)

Induction
- Anthracycline (3 d) plus cytarabine (7 d, IVCI)

Post-remission therapy
- Intensive chemo
- Auto BMT
- Allo BMT

AML: Induction

- 3 d of idarubicin (12 mg/m²) or daunorubicin (45 mg/m²) better than doxorubicin; higher dauno doses (90 mg/m²) may be better per results of ECOG study
- Add 6-mercaptopurine (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
- Daunorubicin 90 mg/m²/d better than 45 mg/m²/d: survival benefit in some subgroups (non-FLT3 mut, lower WBC).

CALGB: DFS Benefit Only in Patients < 60 Years Receiving High-Dose ara-C

<table>
<thead>
<tr>
<th>Patients in Remission (%)</th>
<th>Age &lt; 60</th>
<th>Age &gt; 60</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 g/m² x 31</td>
<td>80</td>
<td>40</td>
</tr>
<tr>
<td>4 g/m² x 155</td>
<td>80</td>
<td>40</td>
</tr>
<tr>
<td>1.5 g/m² x 155</td>
<td>80</td>
<td>40</td>
</tr>
<tr>
<td>1 g/m² x 155</td>
<td>80</td>
<td>40</td>
</tr>
</tbody>
</table>

AML in CR1: Interaction of ara-C Dose and Cytogenetics

![Graph showing 3-yr DFS for CALGB 8525 study with ara-C doses ranging from 100mg/m² to 3000mg/m² for different cytogenetic subgroups.]

ALLOTX in CR1?

- Prospective trials assigning those with matched sib donors to allotx and others randomized to chemo 'v' allotx
  - Autotx = chemo
  - Allo (low relapse rate) 'v' auto/chemo (low TRM) equivocal (depends on timing, intensity of chemo, allo TRM)
  - Meta-analyses suggest slight benefit for siballo in all but favorable cytogenetics
- 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 allo for highest risk

ALLOTX in CR1?

- Allotx may be a reasonably better option for pts with cytogenetically nl AML, except those with NPM1 mut/FLT3 wt.

AML RX Patients < 60: Guidelines

- Standard induction chemo: 3+7 (60-90 mg/m² of dauno, 100-200 mg/m² of ara-C)
- Post-remission therapy
  - BMT if poor cytogenetics
  - High-dose ara-C in favorable cytogenetics and NPM-1mut/FLT3 wt
  - allo BMT 'v' APSCT 'v' high-dose ara-C in intermediate cytogenetics

Audience Response Question: 45 YO M w AML

- M2 AML w normal cytogenetics
- NPM1 mutation and FLT3 ITD WT
- Achieves CR with standard rx
- Has healthy matched sib
What is most appropriate consolidation?

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

AML: Treatment of Patients > 60

- Induction
  - As in younger adults, 3 d of an anthracycline and 7 d 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 45-90 mg/m²/d x 3 d + cytosine arabinoside 100-200 mg/m²/d by continuous infusion for 7 d²
- 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 +/- comorbid disease
  - Adverse cytogenetics
  - Antecedent hematological disorder

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Low dose Chemotherapy in Older Poor Prognosis Patients with AML

- Clofarabine 30 mg/m² qd, d1-5 (n = 112) (nucleoside analogue)¹
  - Median age = 71 years, 36% with prior MDS
  - 38% CR, 8% CRp (seen even with several risk factors)
  - Early death rate = 10%
- Decitabine 20 mg/m² qd d1-5 (n = 55) (DNAMTi)²
  - Median age = 74 years, 42% secondary AML
  - 24% CR, 2% CRp
  - Early death rate = 4%
- Cloretazine 600 mg/m² x1 (n = 140) (alkylating agent)³
  - No secondary AML
  - 37% CR + CRp rate
  - Early death rate = 14%

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Post-remission Therapy in Older Patients with AML

<table>
<thead>
<tr>
<th>CALGB 8525</th>
<th>5-Year Disease-free Survival</th>
<th>Overall Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytosine arabinoside*</td>
<td>≤ 14%</td>
<td>8%</td>
</tr>
<tr>
<td>100 mg/m²/d on d 1-5 x 4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>400 mg/m²/d on d 1-5 x 4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3mg/m² q12h on d 1,5,5 x 4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>*Followed by 4 cycles daunorubicin x 1 day + cytosine arabinoside x 5 days</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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Clinical TRIAL PREFERRED (or low dose chemo)

- Especially if v high risk features (eg, age > 70, PS = 2, adverse cytogenetics, comorbid disease)
- Daunorubicin (45-90 mg/m² on days 1-3) + cytosine arabinoside (100-200 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 x 5 d) in the post-remission setting
- Consider consolidation with RIC allo on trial

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Treatment of Acute Promyelocytic Leukemia

- NEED TO KNOW:
  - Document disease
    - Cytogenetics or FISH for t(15;17) (variants rare, but are unresponsive to ATRA)
    - RT-PCR for PML-RARα
  - Risk assessment
    - WBC > 10K = high risk
    - WBC < 10K, plt > 40K = low risk
  - Is patient an anthracycline candidate

- Disease Features
  - Low WBC, DIC, CD33+, HLA-DR-
  - DIC (d.t. 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
**Treatment of Acute Promyelocytic Leukemia**

- **Induction:**
  - ATRA alone leads to non-durable CRs via diff.
  - Anthracycline (dauno or ida) x 3-4d (+/-) cytarabine plus ATRA (until CR) is best
    - Treat ATRA-differentiation syndrome (hypoxemia, third-spacing, occurs in up to 25%) with dexamethasone x 3 d, hold ATRA
- **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 LP96 and LPA99**

- IDA+ ATRA induction
  - Best px: WBC < 10; plt > 40
- 3 cycles (risk adapted in later trial) consolidation (anthracycline/ATRA)
- 1 year of ATRA/antimetabolite rx maintenance
- N = 732
  - 91% CR rate
  - 11% relapse rate at 5 years if ATRA in consolidation for int and hr


**PETHEMA LPA 99 Trial (no A2O3)**

**PETHEMA LPA 99 ‘v’ APL 2000 (French w. ara-C)**

**Event-free Survival**

- Low risk: 86% CR rate
- Intermediate: 82% CR rate
- High risk: 56% CR rate
- Median follow up 56 mo


**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 (d 1 to CR) dauno (d 3-6) ara-C (d 3-9)
- CR patients are randomized to receive:
  - As2O3 0.15 mg/kg/d IV x 25 d x 2 cycles plus dauno/ATRA x 2
  - OR dauno/ATRA x 2 alone
- 2nd randomization to:
  - ATRA 45mg/m2 po x 7 d every other week x 1 yr
  - OR ATRA 45mg/m2 po x 7 d every other week plus MTX/6-MP x 1 yr

ASCO 2007- Arsenic: better DFS and OS

**ALL: Therapy**

- Childhood ALL: 85% cured; the great success story based on anthracycline, vincristine, steroid, L-asparaginase induction; CNS prophylaxis; intensification; and POMP maintenance

- Adult ALL: 35% cured; more difficult biology (increased incl 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
  - Early results from DFCI, Spain, and France suggest that pediatric regimens applied to adults up to age 30-40 work ‘better’ than adult regimens

**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/daunorCVC/L-asparaginase/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)
  - Large prospective trial (ECOG/MRC) suggest allo tx best for those under 35

**Event-free Survival by Age: ATRA/Arsenic for APL**

**ATRA+As$_2$O$_3$ in Untreated APL: Treatment Design and Monitoring**

**Induction**
- ATRA 45 mg/m$^2$/d po until CR
- As$_2$O$_3$ 0.15 mg/kg/d IV D10 until CR
- Gemtuzumab ozogamicin (GO) 9 mg/m$^2$ D1, if WBC > 10x10$^9$/L

**Maintenance**
- As$_2$O$_3$ 0.15 mg/kg I.V. 5d/wk x 4 wks
  - 1 month on, 1 month off x 3; total doses, 60
- ATRA 50 mg/m$^2$/d po
  - 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

**CALGB 9710: DFS By RX and WBC**

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

<table>
<thead>
<tr>
<th>Cooperative Group</th>
<th>Study Period</th>
<th>Age (yrs)</th>
<th>CR (%)</th>
<th>EFS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>North America (Stock)</td>
<td>1988-1998</td>
<td>16-21</td>
<td>96%</td>
<td>66%</td>
</tr>
<tr>
<td>CCG (peds)</td>
<td>196 pts</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CALGB (adults)</td>
<td>103 pts</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>French (Boissel)</td>
<td>1993-1994</td>
<td>15-20</td>
<td>94%</td>
<td>67%</td>
</tr>
<tr>
<td>FRALLE (peds)</td>
<td>77 pts</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LALA (adults)</td>
<td>100 pts</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dutch (deBois)</td>
<td>1985-1999</td>
<td>15-21</td>
<td>98%</td>
<td>69%</td>
</tr>
<tr>
<td>SKION (peds)</td>
<td>47 pts</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HOVON (adults)</td>
<td>73 pts</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Italian (Testi)</td>
<td>1996-2000</td>
<td>14-18</td>
<td>94%</td>
<td>83%</td>
</tr>
<tr>
<td>AIEOP (peds)</td>
<td>153</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GIMEMA (adults)</td>
<td>95</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### 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 d 1, dauno 30 mg/m² d 1-3, prednisone
    - 60 mg/m² d 1-7, VCR 2 mg d 1,8,15, 22 and L-asparagine 6000 U/m² 2x/week
    - G-SCF on d 4 if ANC recovery is beneficial (CALGB 9011)
- Intrinsic biologic Hurdle: High incidence of PH + ds in this age cohort
  - Good short term results with dasatinib and steroids (Foa, ASH, 2008)

### 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); MD Anderson 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 o/w hyperCVAD hist controls
    - 3 yr DFS of 66 v 14%; OS: 55% v 15%
    - Some relapsed (28% relapse rate over 52 months) with TKD mutations, suggesting role for newer TKIs

### Audience Response Question: 71 yo M w MDS

- WBC=1.5K, plt=21K , 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
  - Comorbid 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 Variable</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marrow blasts (%)</td>
<td>0.5</td>
</tr>
<tr>
<td>Good</td>
<td>1.0</td>
</tr>
<tr>
<td>Intermediate</td>
<td>1.5</td>
</tr>
<tr>
<td>Poor</td>
<td>2.0</td>
</tr>
</tbody>
</table>

#### Prognostic Variable
- 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
- Intermediate = other karyotypes
- Poor = chromosome 7 abnormalities or complex

#### Cytopenias
- Hb < 10 g/dL, ANC < 1800/uL, platelets < 100,000/uL

### WPSS Risk Group

<table>
<thead>
<tr>
<th>WPSS Risk Group</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very Low</td>
<td>0</td>
</tr>
<tr>
<td>Low</td>
<td>1</td>
</tr>
<tr>
<td>Intermediate</td>
<td>2</td>
</tr>
<tr>
<td>High</td>
<td>3-4</td>
</tr>
<tr>
<td>Very High</td>
<td>5-6</td>
</tr>
</tbody>
</table>

### Allogeneic Marrow Transplantation in MDS

- "Only known curative modality"
- HLA-matched sibling or unrelated 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

### AlloTX in MDS: Approximation of Life Expectancy (Years)

<table>
<thead>
<tr>
<th></th>
<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>
<td>7.21</td>
</tr>
<tr>
<td>Int-1</td>
<td>4.61</td>
<td>4.74</td>
<td>5.16</td>
</tr>
<tr>
<td>Int-2</td>
<td>4.93</td>
<td>3.21</td>
<td>2.84</td>
</tr>
<tr>
<td>High</td>
<td>3.20</td>
<td>2.75</td>
<td>2.75</td>
</tr>
</tbody>
</table>


### 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

### Hematopoietic Growth Factors 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
  - Most effective in RARS

- Very limited role for G-CSF as a single agent (recurrent pyogenic inf'ns) and no ‘platelet GF’, though romiplostim (TPO agonist) being developed

### 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

### Immunosuppression in MDS

- Theory that the pathophysiology of cytophenias 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)
    - Best chance: younger pts and lower plt counts, HLA-DR15

### “Immunomodulatory” Therapy in MDS

- Thalidomide (first imid used) (n = 1, 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 Sq- patients (Approved); 26% rate of RBC tx indep in non-Sq- (off-label use)
  - Indolent histology (low and int-1, and preserved ANC and plt only)
  - SE’s: low blood counts (may be ‘treatment’ effect)

### Developing New Therapies in MDS: Differentiation

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)

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

1) Supportive Care
   - Exit Criteria
   - No Continue until Endpoint
   - Yes Azac C
     - (dose as per arm #2)
   - Response - Continue Rx
   - No Response - Off Study

QOL: Quality of Life Assessment
M = Bone Marrow     Aza C – Azacitidine S.C.

Time to AML Transformation

- Azacitidine
- Supportive Care

Probability of Remaining Event-Free

0.0 0.2 0.4 0.6 0.8 1.0
0 6 12 18 24 30 36 42 48 54

p=.001
p=.007

Response in 60% (7% CR, 16% PR, 37% HI)

Survival: FAB Classification

- Azac/Low
- Supp Care/Low
- Azac/High
- Supp Care/High

Azacitidine Survival Study

Survival Study Design

- Patients Randomized into Study (higher risk)
  - Azacitidine 75 mg/m² 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 = 0.0001)
  - 9.4 months median survival benefit for patients on azacitidine compared with CCR
  - Formal response criteria need not be met to note survival benefit
  - 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.
  - Recent randomized trial ‘v’ supportive care: no survival benefit (ASH 2008)
  - New schedule in common use: 20 mg/m²/d x5 d

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); add low dose G-CSF in RARS
- Lenalidomide in 5q-
- Clinical trial if possible; if not
  - Consider ATG
  - Consider 5-aza/decitabine in all others (aza in high risk)

Audience Response Question: 71 yo M w MDS

- WBC=1.5K, plt=21K, 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: Conclusions

- 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

Thank you for attending Master Class for Oncologists