Acute Myeloid Leukemia

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Putting the Problem into Perspective

All other sites (~1,445,000)
- AML (~12,000)
- CML (~5,000)
- ALL (~6,000)
- CLL (~15,000)
- Other (~15,000)

Jemal A et al. CA Cancer J Clin 2007; 57: 43-66

Age-Specific Incidence Rates for AML:1995-1999

Etiology and Risk Factors

- Chemical exposure
  Benzene; pesticides
- Other environmental exposures
  Hair dyes; smoking, non-ionic radiation
- Genetic disorders
  Down syndrome; Bloom syndrome; Fanconi’s anemia; ataxia-telangectasia; Wiskott-Aldrich
- Prior chemotherapy or XRT
  Alkylating agents; topoisomerase II inhibitors

Etiology and Risk Factors
Antineoplastic Agents

- Alkylating agents
  - preceding MDS phase
  - evolution to AML after 5 to 7 years
  - chromosome abnormalities: -5, -7
- Topoisomerase II inhibitors
  - no MDS phase
  - short latency of 1 to 3 years
  - monocytic morphology
  - chromosome abnormalities: 11q23

AML Diagnosis

- ≥ 20% blasts (BM and/or PB)
- IHC stains
  - Myeloperoxidase (+) or nonspecific esterase (+) or butyrate esterase (+)
- Immunophenotype (flow cytometry)
  - ≥ 2 myeloid markers (+)
  - < 2 lymphoid markers (+)
- Cytogenetic-molecular

Expression of Cell-Surface and Cytoplasmic Markers in AML Diagnosis

Stage/Lineage | Marker
--- | ---
Percursor | CD34, CD38, CD117, CD133, HLA-DR
Granulocytic | CD13, CD15, CD16, CD33, CD65, cMPO
Monocytic | CD11c, CD14, CD64, lysozyme, CD4, CD11b, CD36, NG2 homologue
Megakaryocytic | CD41 (gp Iib/IIIa), CD61 (gp IIb/IIIa), CD42 (gp Ia)
Erythroid | CD235a (glycophorin A)

CD34 and HLA-DR are negative in APL.

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Cytogenetic Risk Groups

<table>
<thead>
<tr>
<th>MRC</th>
<th>SWOG/ECOG</th>
<th>CALGB</th>
<th>GIMEMA/AML10</th>
<th>German AMLCG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Favorable</td>
<td>t(15;17)</td>
<td>t(16;16)</td>
<td>t(15;17)</td>
<td>t(16;16)</td>
</tr>
<tr>
<td>Intermediate</td>
<td>normal</td>
<td>normal</td>
<td>normal</td>
<td>normal</td>
</tr>
<tr>
<td>Adverse</td>
<td>-5/-6qdel(6q)</td>
<td>-7</td>
<td>other</td>
<td>other</td>
</tr>
</tbody>
</table>

Impact of cytogenetic entities recognized in 2008 WHO classification on survival.

Pre-Treatment Karyotype as Prognostic Factor in AML (CALGB 8461)

![Graph showing karyotype distribution]

AML – WHO Classification (2008)

- AML with recurrent genetic abnormalities
  - t(8;21)(q22;q22): RUNX1-RUNX1T1
  - inv(16)(p13;q22) or t(16;16)(p13;q22): CBFB-MYH11
  - t(15;17)(q22;q22): PML-RARA
  - t(9;11)(p22;q22): MLLT3-MLL
- t(6;9)(p23;q23): DEK-NUP214

The WHO allows the diagnosis of AML regardless of marrow blasts.

- AML with MDS-related changes
- Therapy-related myeloid neoplasms
- AML, NOS (includes FAB, acute myelofibrosis)
- Myeloid sarcoma
- Myeloid proliferations related to Down syndrome
- Blastic plasmacytoid dendritic cell neoplasms

Core Binding Factor (CBF) AML

- Incidence: 5-10%
- Molecular: RUNX1-ETO, CBFB-MYH11
- FAB: 20-25% of FABM2, FABM4eo
- Phenotype (Flow): CD19+, CD56+
- Adverse prognosis: ↑ age, ↑ WBC, CD56+, EML/GS, nonwhite

Byrde JC et al. Blood 2002;100:4325-4336

Byrd JC et al. Blood 2002;100:4325-4336
Monosomal Karyotype (MK) in Patients with AML

- MK: ≥ 2 autosomal monosomies or 1 monosomy with structural abnormalities

> 60 years

≤ 60 years

Normal Karyotype AML (NK-AML)

- NK = CN (cytogenetically normal) AML
- Approximately 45% of AML
- Heterogeneous group of patients
- Abnormalities in certain genes confer prognostic significance in adult patients

Insights Into the AML Genome

- 50 whole genomes + 150 exomes = 200 cases
- Recurrently mutated genes: n = 237
- Significantly mutated genes: n = 23

Mutations in AML and Complementation Groups

“Important” Gene Mutations

<table>
<thead>
<tr>
<th>Mutated Gene</th>
<th>Frequency</th>
<th>Clinical Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>NPM1</td>
<td>AML 25-30%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CN AML 45-64%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Del(9)(q) 35-40%; +8 15%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>FLT3/ITD 40%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>IDH 25%</td>
<td></td>
</tr>
<tr>
<td>CEBPA</td>
<td>CN AML 10-18%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Del(9)(q) 40%</td>
<td></td>
</tr>
<tr>
<td>KIT</td>
<td>CN AML &lt; 10%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CBF AML 25-30%</td>
<td></td>
</tr>
</tbody>
</table>

“Important” Gene Mutations

<table>
<thead>
<tr>
<th>Mutated Gene</th>
<th>Frequency</th>
<th>Clinical Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>FLT3-ITD</td>
<td>AML 20%</td>
<td>CN AML 28-34%</td>
</tr>
<tr>
<td></td>
<td>- Inferior outcome especially when high mutant/allelic ratio</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Available inhibitors</td>
<td></td>
</tr>
<tr>
<td>FLT3-TKD</td>
<td>AML 5-10%</td>
<td>CN AML 11-14%</td>
</tr>
<tr>
<td></td>
<td>Inv(16) 14-24%</td>
<td></td>
</tr>
<tr>
<td>IDH1, IDH2</td>
<td>AML 15-20%</td>
<td></td>
</tr>
</tbody>
</table>


**Molecular Prognosis in CN AML**


**Correlation of Cytogenetic and Molecular Data in AML with Clinical Data (ELN)**

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>Genetic Lesion</th>
</tr>
</thead>
<tbody>
<tr>
<td>FAVORABLE</td>
<td>t(8;21), inv(16) or t(16;16)</td>
</tr>
<tr>
<td></td>
<td>NPM1***/FLT3-ITD*** (CN)</td>
</tr>
<tr>
<td></td>
<td>CEBPA***/FLT3-ITD*** (CN)</td>
</tr>
<tr>
<td>INTERMEDIATE-I</td>
<td>NPM1***/FLT3-ITD***</td>
</tr>
<tr>
<td></td>
<td>NPM1***/FLT3-ITD***</td>
</tr>
<tr>
<td></td>
<td>NPM1***/FLT3-ITD***</td>
</tr>
<tr>
<td>INTERMEDIATE-II</td>
<td>t(9;11), MLL3-MLL</td>
</tr>
<tr>
<td></td>
<td>Other (neither favorable nor adverse)</td>
</tr>
<tr>
<td></td>
<td>inv(3) or t(3;3), RPN1-EVI1</td>
</tr>
<tr>
<td></td>
<td>t(6;9), DEK-NUP214</td>
</tr>
<tr>
<td></td>
<td>t(11;11), MLL rearranged</td>
</tr>
<tr>
<td></td>
<td>-5 or del(5q), -7, abl(17p); complex CG</td>
</tr>
</tbody>
</table>

**Outcome in Younger (A,C,E; age 18 to 60 years) and Elderly (B,D,F; age > 60 years) Patients with AML by ELN Categories**

**2017 European LeukemiaNet (ELN) Recommendations for AML**

**Molecular Markers and Response**

- ECOG E1900 trial – HD daunorubicin was associated with an improved rate of survival among patients with mutant DNMT3A (in UVA also mutant MLL and NPM1)

**FLT3 kinase inhibitors**

- Lestaurtinib
- Midostaurine
- MLN-518
- Sunitinib
- Sorafenib
- AC220

**FLT3 kinase inhibitors**

- Döhner H, et al. JCO 2011;29:2758-2765
- Röllig C et al. JCO 2011;29:2758-2765
- Röllig C et al. JCO 2011;29:2758-2765
(A) EFS, (B) RFS, and (C) OS 
(B)censored and not censored for AlloSCT

Complete Response Rates

<table>
<thead>
<tr>
<th></th>
<th>MIDO (N=360)</th>
<th>PBO (N=357)</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR by day 60</td>
<td>212</td>
<td>191</td>
<td></td>
</tr>
<tr>
<td>Rate</td>
<td>59%</td>
<td>53%</td>
<td>0.15</td>
</tr>
<tr>
<td>Time to CR, median (range)</td>
<td>35 days (20-60)</td>
<td>35 days (20-60)</td>
<td></td>
</tr>
<tr>
<td>CR in induction/consolidation**</td>
<td>239</td>
<td>211</td>
<td>0.045</td>
</tr>
<tr>
<td>Rate</td>
<td>66%</td>
<td>59%</td>
<td></td>
</tr>
<tr>
<td>Time to CR, median (range)</td>
<td>37 days (20-99)</td>
<td>36 days (20-112)</td>
<td></td>
</tr>
</tbody>
</table>

* 2-sided Fisher’s Exact p 
** includes all CRs reported within 30 days of ending protocol therapy

Overall Survival (Primary Endpoint)

- 23% reduced risk of death in the Mido arm
- Median OS: Mido 74.7 (31.7-NE); PBO 25.6 (18.6-42.9) months
- NE: not estimable
- Hazard Ratio*: 0.77
- 1-sided log rank p-value*: 0.0074

IDH mutations lead to 2HG production

- Wild-type IDH1 and IDH2 are NADP+ dependent metabolic enzymes that catalyze isocitrate to αKG
- IDH Mutations cause a reverse reaction that reduces αKG to 2HG via conversion of NADPH to NADP+
- IDH1 and IDH2 Mutations occur in 15-20% of patients with AML

Yen, KE, Oncogene, 2010, 29, 6409-17

RATIFY Schema

Stratification: TKD; ITD with allelic ratio <0.7 'vs' ≥0.7

AG221

- Duration of treatment and best overall response in all response-evaluable patients as of 1 May 2015 (n=158)
- Treatment duration: 3-month = 61.2%; 6-month = 48.7%; Median = 5.6 months

Stein E, et al. ASH 2015

Stone R, et al. ASH 2015, Abstract #6
IDH mutations, BCL-2 Dependence and ABT-199

The large # of pro-apoptotic molecules bound and sequestered by BCL2 has cancer cells “primed” for cell death; apoptosis initiated after displacement by ABT199

Konopleva et al, ASH 2014

Venetoclax Binds to and Inhibits Overexpressed BCL-2

Venetoclax

BH3-only

BAX

BAK

BCL-2

Mitochondria

An Increase in BCL-2 Expression Prevents Cancer Cell Death

Mitochondria

Apoapoptotic

Mitochondria

Mitochondria

Apoptosis is Initiated

Apoptosome

APAF-1

Cytochrome C

Active Caspase

Procaspase

Mitochondria

IDH Mutations and BCL2-Dependence

CR/CRi

IDH1/IDH2 mutation, FLT3 WT or TKD

IDH1/IDH2 mutation, FLT3 ITD

ABT-199 (Venetoclax) for R/R AML:

• 28 evaluable patients, 11 (35%) with IDH1/2 mutations.
• > 50% patients had clinical benefit including 6 CR/CRi; 4 were IDH mutants
• Another 4 IDH mutants with MLFS or PR

Konopleva et al, ASH 2014

Time from Diagnosis to Treatment (TDT)

≤ or > 5 days: AML Patients ≥ 60 years

Initial Evaluation

• Patient-specific → Induction mortality
  - Age
  - Comorbidities
  - Performance status
• Disease-specific → Resistance
  - Cytogenetic-molecular
  - AHD (MDS)
  - MDR phenotype?

AML Treatment (Non-APL)

• Induction
  - cytarabine plus anthracycline
• Postremission therapy
  - chemotherapy
  - allo/auto HSCT
• Recommendations may differ by
  - Age (< 60 y vs. ≥ 60 y) ± PS
  - Karyotype/genotype

AML Induction Therapy

Patients < 60 Years

• Infusional cytarabine (100-200 mg/m²) over 24 hrs daily x 7 days
  
  7 PLUS 3

• Anthracycline *
  - Daunorubicin 60-90 mg/m² iv daily x 3
  - Idarubicin 12 mg/m² iv daily x 3


AML Induction Therapy
(Patients < 60 Years)

- HD daunorubicin prolongs survival *
  - patients < 50 yrs
  - favorable/intermediate CG
  - Absence of FLT3-ITD
- Extension of 3+7 → 3+10
- Addition of 3rd drug
- G/GM priming
- MDR modulators


High-Dose Cytarabine in Induction
(Patients < 60 Years)

- Studies:
  - SWOG (1996) and HOVON (2011) suggest no
  - Metaanalysis of 4 randomized trails (2006) suggests yes
  - EORTC-GIMEMA (2011) suggests yes (for pts ≤ 45 yrs)
- Common issues:
  - higher mortality/toxicity despite survival benefit (in some)

Simplified Classification of AML

- AML sensitive to conventional chemotherapy
  - CBF leukemias (without c-KIT mutation)
  - Diploid AML with NPM1 and CEBPα mutation (without FLT3 mutation)
  - Others (younger patients without AHD)?
  - Dose intensification of chemotherapy may be helpful
- Chemo-resistant AML
  - AML with adverse cytogenetics
  - AML with FLT3-ITD
  - Others (older patients, younger patients with t-AML and/or AHD)
  - New agents are needed

Gemtuzumab Ozogamycin in induction Therapy
Meta-analysis of 5 Randomized Trials

- 5:1 molar ratio of cytarabine to daunorubicin is optimal in in vitro and in vivo AML models
- 100-nm bilamellar liposomes
- CPX-351 liposomes deliver 5:1 molar ratio for >24 h
- CPX-351 accumulates and persists in the bone marrow
- Selective uptake of CPX-351 by leukemia blasts and intracellular drug release

Overall Survival Was Greater in the CPX-351 Arm Compared to the 7+3 Arm


Cytarabine/Daunorubicin Liposome: CPX 351
Assessment of Response

- Marrow at d 7-10:
  - assess blasts and cellularity
  - if hypoplastic (cellularity < 20% and blasts < 5-10%) rpt marrow in 7-14 d
  - if ↑ blasts: donor search/salvage Rx

- Goal: complete remission:
  - ANC > 1,000/mcl
  - Plts ≥ 100,000/mcl
  - Marrow blasts < 5%

- Molecular CR only matters in APL

AML Postremission Therapy

<table>
<thead>
<tr>
<th>Better-risk karyotype</th>
<th>HiDAC 3g/m² over 3h q12 d 1,3,5 x 4 * OR HiDAC x 1-2 ⇒ auto HSCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intermediate-risk karyotype</td>
<td>Matched sibling or auto HSCT OR HiDAC 3g/m² over 3h q12 d 1,3,5 x 4 * OR Clinical trial</td>
</tr>
<tr>
<td>Poor-risk karyotype AHD t-AML</td>
<td>Clinical trial OR Allo HSCT/alternative donor HSCT</td>
</tr>
</tbody>
</table>


Indications for Allo SCT in CR1

<table>
<thead>
<tr>
<th>Genotype</th>
<th>MSD</th>
<th>Alternative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Favorable</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>+ KIT</td>
<td>Possible</td>
<td>Possible</td>
</tr>
<tr>
<td>Intermediate</td>
<td>Possible</td>
<td>Possible</td>
</tr>
<tr>
<td>+ FLT3/ITD</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>+ NPM1 w/o FLT3/ITD or IDH1</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>+ CEBA* w/o FLT3/ITD or IDH1</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Unfavorable</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

* Biallelic mutations only

Modified from Rowe JM, Talman ML. Blood 2010; 116: 3147-3156

AML Survival Expectations

ECOG 1973-1997

AML Induction Therapy

(Patients ≥ 60 Years)

- Ara-C + Anthracycline induction
  - PS 0-2; no significant comorbidities; absence of unfavorable disease features

- Alternative approaches
  - intermediate intensity therapy (clofarabine)
  - low-intensity therapy (hypomethylating agents; low dose cytarabine)
  - best supportive care (hydrea, transfusions)
  - palliative care

AML Therapy for Patients ≥ 60 Yrs

- Assess performance status, comorbidities and karyotype
- Preferably, obtain karyotype/molecular profile prior to therapy
- Standard induction not appropriate
  - pts ≥ 70 - 75 yrs
  - poor PS (> 2)
  - poor risk karyotype


Modified from Rowe JM, Talman ML. Blood 2010; 116: 3147-3156
Postremission Surveillance

- **CBC and platelets**
  - every 1-3 months x 2 years
  - then every 3-6 months x 3 years

- **Marrow**
  - only if hemogram becomes abnormal
  - no routine surveillance recommended

- **Minimal residual disease**
  - only in the context of clinical trials

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MRD: Available Techniques

- Quantification of MRD provides an estimate of the reduction of disease burden, reflecting:
  - the inherent leukemia biology
  - drug-resistance mechanisms
  - the adequacy of the treatment, and
  - other host-drug interactions influencing the response.

| Table 1: Currently Available Techniques for Minimal Residual Disease Monitoring |
|-----------------|-----------------|----------------|------------------|
| Method          | Target           | Sensitivity    | Strength and Weaknesses | Reference |
| Cytogenetics    | Chromosomal alterations | 1 in 20 (5%) | Interactive, cheap, widely available | 62 |
| Flow cytometry  | Leukemia associated aberrant immunophenotype | 1 in 10,000 (0.01%) | Applicable to most AML cases | 6,7 |
| RQ-PCR          | Fusion transcript, gene mutations, overexpressed genes | 1 in 1,000,000 (0.001%) | Highly sensitive | 6,7 |

Abbreviations: AML, acute myeloid leukemia; RQ-PCR, real-time quantitative polymerase chain reaction.

Also, Next Generation Sequencing

Ravandi F and Jorgensen J. JNCCN, 2012, 10(8), 1029

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(A) RFS and (B) OS by cytogenetic status at CR and cytogenetic risk at diagnosis

Chen Y, et al. JCO 2011;29:2507-2513

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Minimal Residual Disease in Peripheral Blood after the Second Cycle of Chemotherapy and Clinical Outcomes.


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MRD Assessment – Flow Cytometry

Terwijn M et al. JCO 2013;31:3889-3897

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Effect of MRD Status by FC on Patients in CR after course 1

Freeman S D et al. JCO 2013;31:4123-4131
Agents to Eradicate MRD
- Monoclonal antibodies
  - SGN-CD33A, AMG-330, SL-140
- Demethylating agents
  - Oral azacytidine
- Check-point inhibitors
  - Nivolumab
- Small molecule inhibitors
  - FLT3 Kinase inhibitors, IDH inhibitors, ABT-199
- Vaccines
- CAR-T cells

AML Salvage
- No defined standard
- Determine by age and remission duration
- Remission durations ≥ 12 mos:
  - CR ~ 60%
  - re-induce; clinical trial; HSCT in CR2
- Remission durations < 12 mos:
  - CR ~ 10-20%
  - clinical trial; best supportive care for older pts

Representative Salvage Chemotherapy Regimens (NCCN)
- Cladribine + cytarabine + GCSF ± mitoxantrone or idarubicin
- High-dose cytarabine + anthracycline
- Fludarabine + cytarabine + GCSF ± idarubicin
- Mitoxantrone + etoposide + cytarabine (MEC)

Strongly consider clinical trial in AML relapse

Prognostic Markers of AML in First Relapse
- 667 pts (non-APL) in first Relapse

<table>
<thead>
<tr>
<th>% OS</th>
<th>1-y</th>
<th>5-y</th>
<th>%CR2</th>
</tr>
</thead>
<tbody>
<tr>
<td>70</td>
<td>46</td>
<td>85</td>
<td></td>
</tr>
<tr>
<td>49</td>
<td>18</td>
<td>60</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>4</td>
<td>34</td>
<td></td>
</tr>
</tbody>
</table>

Low score-high OS

Clonal Evolution of AML by Molecular Profiling

Acute Promyelocytic Leukemia
- Incidence 10-15% (FAB M3)
  - higher in hispanics (20-25%) and with ↑ BMI
- Median age at Dx 40 yrs
- Coagulopathy and hemorrhage
  - ↑ Promyelocytes:
    - strongly MPO (+); multiple Auer rods
    - CD9 (+), CD13 (+), CD33 (+), CD34 (-), HLA-DR (-)
- Translocation t(15;17) with PML/RAR-α fusion transcripts
Acute Promyelocytic Leukemia
Two morphologic variants

Hypergranular
- 80% of APL
- “faggot cells”

Microgranular (M3v)
- 20% of APL
- ↑ WBC

Early Death Rate in APL (SEER Data)

- 1400 pts with APL Dx 1992-2007
- Death rate 17.3% (age ≥ 55 yrs 24.2%, p<.0001)
- 3-yr overall survival (age ≥ 55 yrs 47%, p<.0001)
  - 55% if Dx 1992-1995
  - 66% if Dx 1996-2002
  - 70% if Dx 2002-2007
- Cox proportional hazards model
  - only diagnostic time period and age were significant for survival

Randomized Trial - Treatment

ATRA+ ATO - Event-free Survival
Primary endpoint

ATRA + ATO - Overall Survival

ATRA + ATO – Longer follow-up