


## Acute Myeloid Leukemia

---

- Historical Milestones
- Modification of Therapy
  - Molecular Mutations
  - Minimal Residual Disease
- Advances in Therapy
  - Induction
  - Elderly
  - Acute Promyelocytic Leukemia
- Novel Agents

---

 **MD Anderson Cancer Center** A Comprehensive Cancer Center Designated by the National Cancer Institute

---

---

---

---

---

---

---


---

## Disclosure Information

---

**I have no financial relationships to disclose relevant to the content of this presentation**

---

 **MD Anderson Cancer Center** A Comprehensive Cancer Center Designated by the National Cancer Institute

---

---

---

---

---

---

---


---

## Milestones in AML

---

1957: Allogeneic Transplant	1988: ATRA
1963: Platelet Transfusion	1997: As <sub>2</sub> O <sub>3</sub>
1969-72: Daunomycin + Ara-C	1998: Reduced Intensity allo SCT
1979: Graft vs. Leukemia	2004: Gene expression profiling
1983: HiDAC consolidation	2008: Cytogenetics + molecular mutations

---

 **MD Anderson Cancer Center** A Comprehensive Cancer Center Designated by the National Cancer Institute

---

---

---

---

---

---

---

---

### Monosomal Karyotype in AML: A Better Indicator of Poor Prognosis Than a Complex Karyotype.

Breems, DA JCO 2008;26:4791

Group	n	Deaths
CBF	214	96
CM	1,002	631
NR	530	408
MK	184	179

*Northwestern University Cancer Center*  
A Comprehensive Cancer Center Designated by the National Cancer Institute

---

---

---

---

---

---

---

---

### AML: Multistep Pathogenesis

<b>Class I Mutation</b> Promote proliferation	<b>Class II Mutation</b> Block differentiation
Examples: BCR/ABL FLT3-ITD ERG	PML/RAR $\alpha$ NPM-1 CEBPA

*Northwestern University Cancer Center*  
A Comprehensive Cancer Center Designated by the National Cancer Institute

---

---

---

---

---

---

---

---

### FLT-3 Receptor

*Northwestern University Cancer Center*  
A Comprehensive Cancer Center Designated by the National Cancer Institute

---

---

---

---

---

---

---

---

### Molecular Markers and Prognosis in AML

---

Gene	
Favorable mutations	NPM1 CEBPA
Unfavorable mutations	FLT3-ITD MLL-PTD WT-1 KIT
mRNA overexpression with unfavorable prognosis	BAALC, ERG MN1, EVI-1

---

**MD Anderson Cancer Center** A Comprehensive Cancer Center Designated by the National Cancer Institute

---

---

---

---

---

---

---

---

---

---

---

---

### Prevalence of EVI1 Overexpression (OE) and Its impact on Diagnosis and Prognosis in AML

(L. Vazquez)

---

- EVI1 OE through 3q26 or other mechanisms is associated with a poor prognosis
- EVI1 was highly expressed in 19% of pts (N=490)
  - 72% (35/48) with 3q aberrations
  - 73% (11/15) with 11q23 translocation
  - 45% (10/22) with monosomy 7
  - 6.5% (11/167) with normal cytogenetics
  - None in Runx1 mutations, trisomy 8, or FLT3-ITD

---

**MD Anderson Cancer Center** A Comprehensive Cancer Center Designated by the National Cancer Institute

---

---

---

---

---

---

---

---

---

---

---

---

### Mutation and Treatment Outcome in Cytogenetically Normal AML

---

- Multivariate analysis of 521 patients in CR with  $\geq$  molecular marker analyzed

Risk Factor	Hazard Ratio (95% CI)
<b>Relapse or death during CR</b>	
Mutant CEBPA	0.48 (0.30-0.75)
Mutant NPM1 without FLT3-ITD	0.44 (0.32-0.61)
MLL-PTD	1.56 (1.00-2.43)
Family donor available	0.60 (0.44-0.82)
<b>Death</b>	
Mutant CEBPA	0.50 (0.30-0.83)
Mutant NPM1 without FLT3-ITD	0.51 (0.37-0.70)
10-year increase in age	1.33 (1.16-1.53)

---

Schlenk R, et al. *N Engl J Med*. 2008;358(19): 1909-1918

**MD Anderson Cancer Center** A Comprehensive Cancer Center Designated by the National Cancer Institute

---

---

---

---

---

---

---

---

---

---

---

---



### Minimal Residual Disease in Acute Leukemia

---

- **Speed of cyto-reduction**  
 Day 6 marrow (J. Holowiecki):
 

<b>&lt;5% Blasts</b>	<b>&gt;5%</b>	<b>P</b>
CR 86%	33%	<.00001
OS 63%	33%	.0009
- **Depth of remission**  
 Cytogenetics  
 Flow cytometry  
 Polymerase Chain Reaction

---

**MD Anderson Cancer Center** A Comprehensive Cancer Center Designated by the National Cancer Institute

---

---

---

---

---

---

---

---

---

---

---

### Minimal Residual Disease (MRD) Assessed by NPM1 Mutations

---

- **S. Schnittger:**  
 NPM1 is more reliable than cytogenetics to detect relapse  
 Early molecular response (within 21-60 days) is not relevant for survival  
 MRD is the most relevant prognostic marker (P<0.001) followed by age (P=0.003) and pretreatment FLT3-ITD (P=0.065)
- **J. Kronke**  
 Achievement of RQ-PCR negativity during consolidation was associated with superior 2yr RFS:76.8% vs. 29.0% for pts with persistent RQ-PCR positivity (P=0.004)

---

**MD Anderson Cancer Center** A Comprehensive Cancer Center Designated by the National Cancer Institute

---

---

---

---

---

---

---

---

---

---

---

### Predictive Value of Minimal Residual Disease (MRD) Monitoring by RQ-PCR in *WT1* positive AML (UK MRC AML-15 Trial)

---

J Liu-Yin

- A greater log reduction in *WT1* transcripts was associated with a significantly reduced relapse risk even after adjustment for age, WBC, cytogenetics, performance status and de novo/ secondary AML (Hazard ratio of 0.57 per log reduction P<0.0001)

Log Reduction	5 yr relapse rate (%)
<2	77
2 – 3	50
>3	26

---

**MD Anderson Cancer Center** A Comprehensive Cancer Center Designated by the National Cancer Institute

---

---

---

---

---

---

---

---

---

---

---

## Intensifying Induction Therapy in AML

- Idarubicin substituting for daunomycin
- Increasing dose of anthracycline
- Modulation of cytarabine
- Addition of other drugs-etoposide, nucleoside analogs, mylotarg, molecular targets
- Priming with growth factors
- Timed sequential therapy (day 6 – 10)
- Early intensification (day 10 – 21)



A Comprehensive Cancer Center Designated by the National Cancer Institute

---

---

---

---

---

---

---

---

---

---

---

---

## Is there a better Anthracycline in Elderly AML?

ALFA 9801 Study

- 468 newly diagnosed AML patients
  - Ages 50-70 years
- Induction chemotherapy with “7 + 3”, cytarabine 200 mg/m<sup>2</sup> x 7 days and:
  - Daunorubicin 80 mg/m<sup>2</sup> x 3 days versus
  - Idarubicin 12 mg/m<sup>2</sup> x 3 days versus
  - Idarubicin 12 mg/m<sup>2</sup> x 4 days

	Daunorubicin x 3 days	Idarubicin x 3 days	Idarubicin x 4 days	P Value
CR	70%	83%	78%	0.02
3-Yr Incidence of Relapse	69%	63%	62%	NS
3- Yr OS	31%	40%	41%	NS

Pautas C, et al. Blood. 2007;110(11). Abstract 162.



A Comprehensive Cancer Center Designated by the National Cancer Institute

---

---

---

---

---

---

---

---

---

---

---

---

## High Dose Ara-C vs Standard Dose Ara-C during Induction : AML-12 trial of EORTC and GIMEMA Leukemia Groups

(R. Willemze)

### Induction:

- Daunorubicin 50mg/m<sup>2</sup> x 3 days
- Etoposide 50 mg/m<sup>2</sup> x 5 days
- SD-Ara-C (100 mg/m<sup>2</sup> x 10 days) vs HD-Ara-C (3g/m<sup>2</sup>/every 12 hours x 4 days)

Consolidation: Ara-C 500 mg/m<sup>2</sup>/12 hrs x 6 days

Transplant - Auto or Allo Maintenance: IL2 or no

	SD	HD	P
CR	73.6%	80.7%	0.001
DFS	43.4%	44.6%	0.66
Donor	51.8%	47.6%	0.41
No Donor	39.6%	42.9%	0.31



A Comprehensive Cancer Center Designated by the National Cancer Institute

---

---

---

---

---

---

---

---

---

---

---

---

### Ten Year Follow-Up Analysis Comparing Different Mode of Ara-C in AML

(C. Becker)

1 x 2g/m<sup>2</sup>/d Ara-C over 8 hours (250 mg/m<sup>2</sup>/h) vs 2 x 1g/m<sup>2</sup>/d Ara-C over 3 hours (330 mg/m<sup>2</sup>/h)

- Days 1, 3, 5, 7 + idarubicin or mitoxantrone
- 2<sup>nd</sup> consolidation followed by auto or allo SCT or
- 3<sup>rd</sup> consolidation

No differences between Ara-C induction groups in CR (both 69%), early death (11% vs 8%), EFS (both 25%), and overall survival (32% vs 30%)



A Comprehensive Cancer Center Designated by the National Cancer Institute

---

---

---

---

---

---

---

---

---

---

---

---

### Addition of Cladribine to the Standard 7 + 3 Improves Overall Survival in Adult AML

(J. Holowiecki)

	DAC	DA	DAF	
CR	63%	51%	55%	
	P=.01			
				- NS
				P
OS	51%	39%	36%	.03
LFS	51%	32%	41%	NS



A Comprehensive Cancer Center Designated by the National Cancer Institute

---

---

---

---

---

---

---

---

---

---

---

---

### Pilot Study of Intensive Chemotherapy Including Gemtuzumab in Children with AML (N=340)

(J. Franklin)

Induction I: cytarabine (A), daunorubicin (D), etoposide (E):  
10+3+5+GMTZ on day 6

Induction II: ADE: 8+3+5

Intensification I: HiDAC+E

II: Mitoxantrone + A+GMTZ day 7

III: Capizzi II

CR: 87%, Death 2.6%

3 yr EFS = 49% OS = 63%

Risk of relapse with donor = 22% vs 39% without donor (P=0.053)

VOD in 18 (5%) pts: 2 during intensification II, 8 during SCT, 8 during follow-up.



A Comprehensive Cancer Center Designated by the National Cancer Institute

---

---

---

---

---

---

---

---

---

---

---

---

**Older age is an Independent Risk Factor in AML**

(T. Buchner)

≥ 60 yo: 54% of 2734 pts

	≥ 60 yo	<60 yo	P
OS	13%	40%	
RR	82%	52%	
2° AML	29%	17%	<.0001
Unfavorable karyotype	29%	23%	.0004
Favorable karyotype	4%	12%	<.0001
NPM1+/FLT3-ITD-	26%	34%	<.009
CBF leukemia OS	27.5%	69.4%	
NPM1+/FLT3-OS	37.1%	71.9%	



National Cancer Center

A Comprehensive Cancer Center Designated by the National Cancer Institute

---

---

---

---

---

---

---

---

---

---

---

---

**Core Binding Factor Leukemia of the Elderly**

(T. Prebet)

150 Pts > 60 yrs: 88% CR rate

Variable	RR OS	P
High WBC	2.56	.001
ECOG (0-1 vs 2-4)	5.12	<.001
Deletion 9q	5.06	<.001
ICU admission	5.18	<.001
Use of HIDAC	0.37	.003



National Cancer Center

A Comprehensive Cancer Center Designated by the National Cancer Institute

---

---

---

---

---

---

---

---

---

---

---

---

**Hypomethylating Therapy in AML**

- F. Ravandi: Chromosome 5 and 7 abnormalities: 41% CR (5 aza) vs 35% standard chemotherapy, superior OS
- E. Raffoux: 5 aza, valproic acid, ATRA: 35% response rate in high-risk AML/MDS
- L. Maurillo: 5 aza alone or other: 35% response rate, including 16% CR



National Cancer Center

A Comprehensive Cancer Center Designated by the National Cancer Institute

---

---

---

---

---

---

---

---

---

---

---

---

### Hypomethylating Therapy in AML

- A. Cashen: Decitabine (5 days) in 55 elderly pts, median age 74 yr; 26% response-24% CR, 2% CRi; median survival 9.6 mo; 30 day mortality 4%
- W. Blum: Decitabine (10 days): 11/22 (50%) CR, 4 Cri; mortality 18%
- M. Lubbert: 4 cycles of Decitabine (135mg/m<sup>2</sup> over 3 days in 9 IV 3 hour infusions) in 235 pts: 71% CR + PR followed by maintenance
- G. Borthakur: Decitabine + Mylotarg in relapsed MDS/AML: 8/37 (22%) response: 3 CR/CRp (9%)



A Comprehensive Cancer Center Designated by the National Cancer Institute

---

---

---

---

---

---

---

---

---

---

---

---

### Acute Promyelocytic Leukemia: 2008

**A Standard Approach:**

Induction: ATRA + Idarubicin (AIDA)  
 Consolidation: Anthracycline-based for 2-3 cycles  
 Maintenance: ATRA + 6MP + MTX for 1-2 years

**Consider**

Arsenic Trioxide in induction for elderly or cardiac compromise and in consolidation for other pts  
 Intermediate or high dose cytarabine for high risk pts (WBC >10k): higher CR rate (95.1% vs 83.6%, p=.018), lower relapse rate (9.9% vs 18.5%, p=.12), better OS (91.5% vs 80.8%, p=.026)

(L. Ades, Blood 2008;111:1078)



A Comprehensive Cancer Center Designated by the National Cancer Institute

---

---

---

---

---

---

---

---

---

---

---

---

### Risk- Adapted Treatment of APL PETHEMA LPA 2005 Trial

(M. Sanz)

- Low Risk (WBC <10k, Pits >40k): 3 ATRA+ anthracycline consolidations
- Intermediate Risk (WBC <10k, Pits <40k): increased anthracycline
- High Risk (WBC >10k): addition of HiDAC in course 1, additional mitoxantrone course 2, intermediate Ara-c in course 3
- CR= 92%, 2 yr DFS=94%, OS=92%, Relapse 5%: 0% low risk, 6% intermediate risk, 8% high risk



A Comprehensive Cancer Center Designated by the National Cancer Institute

---

---

---

---

---

---

---

---

---

---

---

---



### Clofarabine (CLOF)

- B. Powell: HiDAC→CLOF- 13/37 (43% Response: 14 CR, 2 Cri) in relapsed/refractory AML; median survival 119 days
- P. Becker: G-CSF priming + HiDAC→CLOF in relapsed/refractory AML – 5/8 CR (62%) without prior transplant
- H. Erba: Single agent CLOF in untreated older adult pts with AML: 46% response rate (38% CR, 8% CRp) in 112 pts. 30 day mortality 9.8%. ORR was 42% with unfavorable cytogenetics, 50% with AHD, 32% with ECOG PS 2, and 39% with age ≥ 70 yrs.



A Comprehensive Cancer Center Designated by the National Cancer Institute

---

---

---

---

---

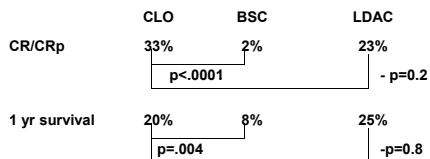
---

---

---

### Cloretazine vs Best Supportive Care (BSC) vs Low Dose Ara-C (LDAC)

(R. Hills)



A Comprehensive Cancer Center Designated by the National Cancer Institute

---

---

---

---

---

---

---

---

### Which AML Subsets Benefit from Leukemic Cell Priming during Chemotherapy?

(X. Thomas)

	CR Rate	P	EFS	P
GM-CSF	88%	.04	43%	.04
no GM-CSF	78%		34%	

- Did not improve outcome in CBF leukemia (61% vs 62%)
- Did improve 5 yr EFS in FLT3-ITD or MLL positive: 39% vs 8%, p=0.005.



A Comprehensive Cancer Center Designated by the National Cancer Institute

---

---

---

---

---

---

---

---

## Voreloxin

- M. Maris: Phase II trial for elderly pts with newly diagnosed AML (N=15): 6/9 evaluable had a blast count <5% on day 22 (3 CR, 3 are in count recovery); 2 deaths within 60 days
- J. Lancet: Phase I trial with cytarabine in relapsed/refractory AML: 7/24 (29%) CR, continuing to dose escalate.

---

---

---

---

---

---

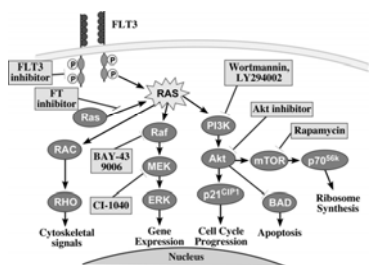
---

---

---

---

## Molecular Pathways in AML




---

---

---

---

---

---

---

---

---

---

## Molecular Targeted Therapy in AML

- Tipifarnib + Bortezomib: (J Lancet, S Paolini)
- Sorafenib + Ida + Ara-C: 22/25 responses (19 CR, 3 Cri) (F Ravandi)
- AC220, a second generation FLT 3 inhibitor, phase I: 11/45 (24%) responses, 4 CR (J Cortes)
- Triciribine, AKT-inhibitor, phase I: reduction in blasts (n=39) (F Ravandi)
- Belinostat, histone deacetylase inhibitor (R Schlenk)

---

---

---

---

---

---

---

---

---

---

## Immune Targeted Therapy in AML

- Cytarabine and Bismuth-213-labeled-HuM195 (T Rosenblatt)
- Anti-CD123 (IL-3R $\alpha$ ): marker for leukemia stem cells (CD34+ 38-) (A Roberts)
- Interleukin-2-Diphtheria toxin (IL-2DT): T reg depletion and blast clearance in AML (C Bucker)



A Comprehensive Cancer Center Designated by the National Cancer Institute

---

---

---

---

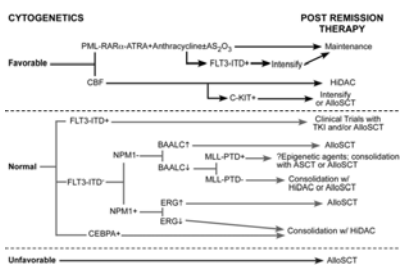
---

---

---

---

## Risk Stratify in AML



A Comprehensive Cancer Center Designated by the National Cancer Institute

---

---

---

---

---

---

---

---