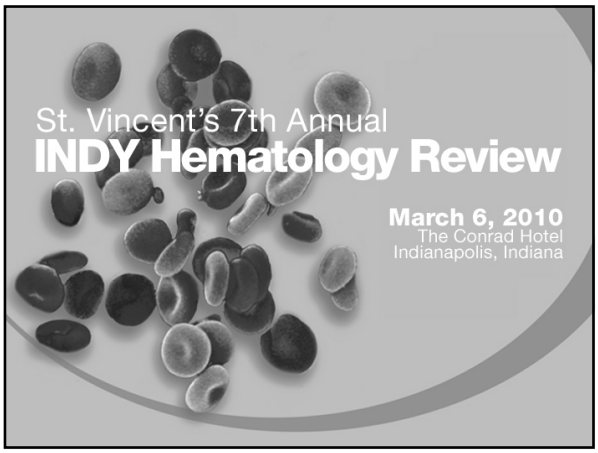

ACUTE MYELOGENOUS LEUKEMIA

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Acute Myelogenous Leukemia

- **Uncommon disease: 13,400 patients/yr in US**
- **Median age: 72 years**
- **Comorbidities common**
- **Therapy-related AML and antecedent hematologic disorders (MDS and MPN) common**
- **Genomic heterogeneity within a specific cytogenetic subtype**

CA for Clinicians, 2007; Juliusson G, et al. **Blood. 2009;113(18):4179-87.**

Topics To Address

- New molecular prognostic factors
- New induction and postremission strategies
- Therapeutic targets for specific genetic subtypes
- New trends in transplant
- What's new that changes practice?

Evolution of Prognostic Factors

- 1970's-1980's: Age, WBC, antecedent hematologic disorder
- 1980's-1990's: Cytogenetics
- 1990's-2000's: Molecular genetics (*FLT3, NPM1, c-KIT)*
- 2000's-2010's: Interactions between genes (*FLT3 and NPM1*), quantitation of genes allelic ratio (*FLT3*); biallelic (*CEBPα);* microRNA

New Prognostic Factors
Molecular Markers

- Mutations in or overexpression of specific genes
- Expressed from cells from patients with normal karyotype
- Unfavorable prognosis: *FLT3, c-KIT, WT1, BAX, BCL-2/BAX, BAALC, EVI1, MLL, ERG, TET2*
- Favorable prognosis: *NPM1, CEBPα*

Frequency of Gene Mutations in Normal Karyotype AML

NPM1	53%
FLT3-ITD	31%
FLT3-TKD	11%
CEBPα	14%
MLL-PTD	8%
NRAS	13%

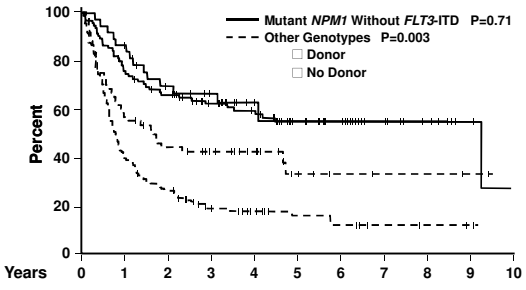
Schlenk RF, et al. N Engl J Med. 2008 May 1;358(18):1909-18.

NPM1 Mutations

- In 45-62% of NK-AML
- Higher blast and platelet counts
- Frequent extramedullary disease, females
- Low CD34 and high CD33 expression
- Frequently assoc. with *FLT3* mutations
- Rarely assoc. with *MLL* or *CEBPα*
- Favorable prognostic marker for RFS and OS in absence of *TET2*

Falini B, et al. N Engl J Med. 2005 Jan 20;352(3):254-66 *Nibourel O, et al. Blood. 2009;114: Abstract 163; Abdel-Wahab O, et al. Blood. 2009;114:144-147.*

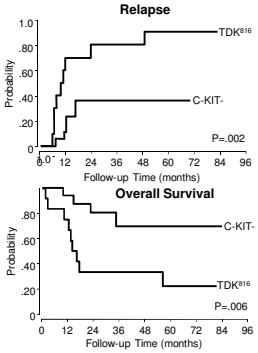
Relapse-Free Survival Untreated AML



Schlenk RF, et al. N Engl J Med. 2008 May 1;358(18):1909-18.

Poor Prognosis t(8;21)

- CD56 expression
- Associated trisomy 4
- Receptor tyrosine kinase pathway mutations in 49%
- *FLT3* and *c-KIT* mutations



Baer MR, et al. Blood. 1997;90(4):1643-8. *Nishii, et al. Leukemia. 2003;* 17(4):731-7. *Nanri, et al. Leukemia 2005,* 19(8):1361-6. *Du Blood 2006 (abstr 2301); Cairoli Blood,* 2006; 107: 3463 - 3468

Ten Eleven Translocation 2 (*TET2*) Mutations

- In 24% young adults with de novo AML
- No assoc. with gender, age, Hgb, plts, FAB, or cytogenetics, FLT3 or CEBPα
- No assoc. with DFS or OS
- Assoc. with *NPM1*: worse DFS if *TET2+* in *NPM1+* patients
- Among NK AML: *NPM1+/FLT3-/TET2-* associated with better DFS and OS than other NK AML (3-yrs 82% vs 37%, 81% vs 42%, p=0.01, p=0.04)

Nibourel ASH 2009 (abstr 108)

Towards a Reclassification of Cytogenetic (and Molecular) Risk Groups

Very favorable	t(15;17) with any abn
Favorable	inv(16) lacking *c-KIT*; t(8;21) lacking del(9q) or complex karyotype or *c-KIT*; normal karyotype *FLT3-/NPM1+/TET2-* or *CEBP*α (double)
Intermediate	Normal or +8 or +21 or others
Unfavorable	-5/del(5q), -7/del(7q), inv(3q), abn of 11q, 20q, 21q, 17p, del(9q), t(6;9), t(9;22), complex karyotypes with ≥ 3 abn; inv(16) or t(8;21) *c-KIT+*; normal karyotype *FLT3+*

Adapted from Slovak Blood 2000; 96: 4075 – 4083. Dohner Blood 2010; 115: 453 – 474.

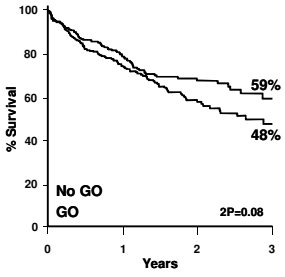
New Induction Strategies

Gemtuzumab Ozogamicin (GO) In Induction

MRC AML15 Schema

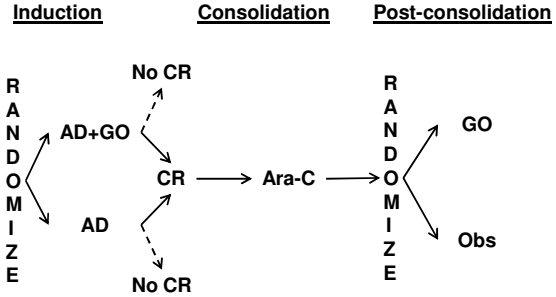
Induction	Consolidation
DA ± GO vs ADE ± GO vs FLAG-Ida ± GO	MACE-MiDAC ± GO vs HiDAC ± GO (3.0 vs 1.5 mg/m²)

AML 15: Overall Survival Favorable/Intermediate-risk



Burnett Blood, 2006 (abstr 13)

SWOG S0106: Phase 3 Randomized Trial of GO in Induction and Maintenance in Untreated AML



Petersdorf ASH 2009 (abstr 790)

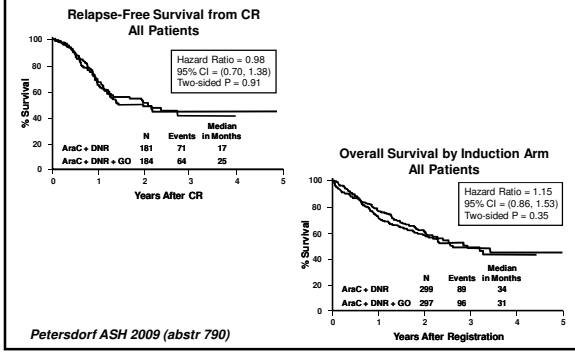
AML Study S0106
Response to Induction Chemotherapy

	Ara-C + DNR + GO (N = 297)		Ara-C + DNR (N = 299)	
	N	%	N	%
CR	184	67%	181	67%
CRi	19	7%	15	6%
PR	2	1%	4	1%
RD	46	17%	57	21%
Early Death *	5	2%	0	0%
Not Assessed	19	7%	12	4%
Pending	22	---	30	---

* Died during aplasia or within 7 days after completing induction

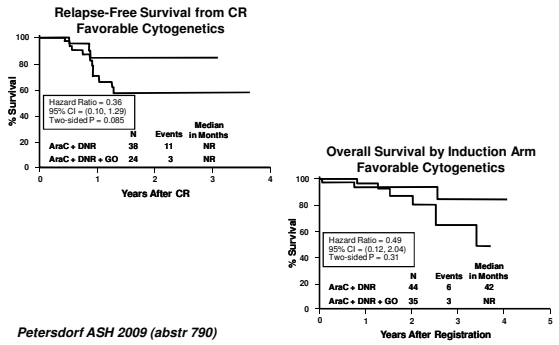
Petersdorf ASH 2009 (abstr 790)

AML Study S0106
Relapse-Free and Overall Survival



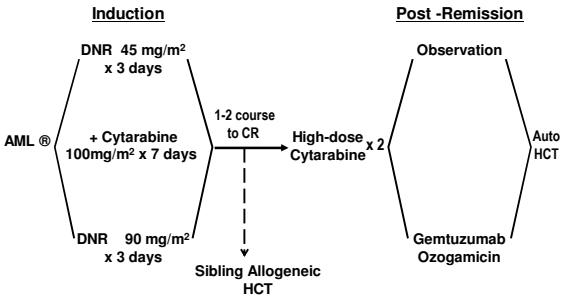
Petersdorf ASH 2009 (abstr 790)

AML Study S0106
Relapse-Free and Overall Survival

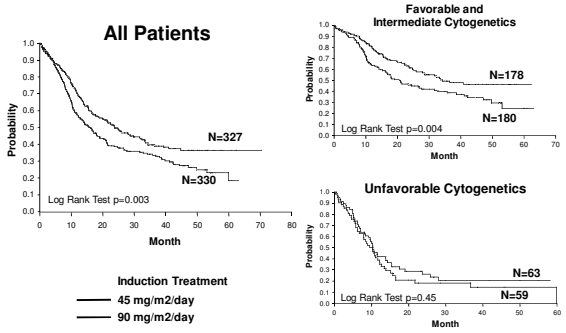


Petersdorf ASH 2009 (abstr 790)

Dauno Dose Intensification: E1900
AML < 60 yrs



Dauno Dose Intensification: E1900
Overall Survival



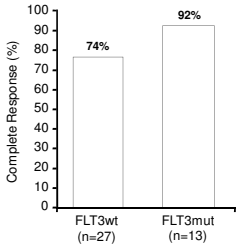
Fernandez N Engl J Med, 2009; 361(13):1249-59

Genetic Subtypes of AML To Which Novel Agents Can Be Directed (Generally In Context of Clinical Trials)

Subtype	Agent(s)
CD33+	GO, DMTIs
FLT3+	FLT3 inhibitors
PML-RARα	ATRA, ATO
C-KIT+	TK inhibitors
RAS+	FT inhibitors
MLL PTD+	HDACIs, DMTIs

FLT3 Inhibitors

Phase 1b trial of PKC412 + chemo in younger pts with newly diagnosed AML



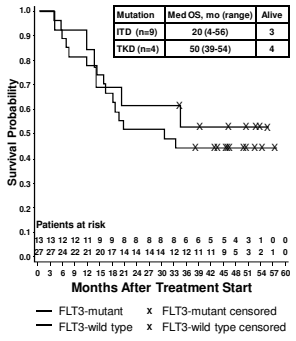
Stone ASH 2009 (abstr 634)

FLT3 Inhibitors

Phase 1b trial of PKC412 + Chemotherapy in younger pts with newly diagnosed AML

	Overall Survival	
	1-yr	2-yr
WT	81%	59%
Mut	85%	62%

Similar Survival Seen in Previously Untreated Patients With FLT3mut and FLT3wt Blasts



Stone ASH 2009 (abstr 634)

AC220: RTK Inhibitor

- **Potent selective second generation FLT3 RTK inhibitor, Phase I trial**
- **Highly selective for both FLT3 mut and WT, activity against KIT**
- **Rel/Ref AML**
- **N=76, 24% FLT3+ and 62% WT, 14% unknown**

Cortes ASH 2009 (abstr 636)

AC220 Phase 1 Response by FLT3 Status

Response	*ITD - (n=45)	ITD + (n=18)	Undetermined (n=13)
PR	6	5	2
CRp	2	0	0
CRi	1	4	1
CR	0	1	1
Response Rate (%)	9 (20)	10 (56)	4 (31)

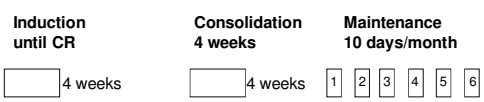
*ITD - = 43 with no mutation identified and 3 TKD (D835 mutation). No responses observed in TKD

Cortes ASH 2009 (abstr 636)

Current Questions in APL

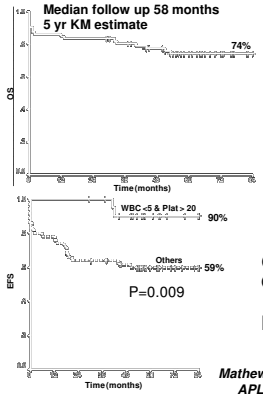
- Can early death rate be reduced? Remains a major problem
  - Early ATRA, before dx confirmed (give in ER)
- What is optimal treatment for high-risk patients?
  - Concomitant ATRA + chemo in induction
  - Either ATO or intermediate-dose ara-C in consolidation
- What is emerging role of arsenic (ATO)?
  - For pts not candidates for chemo
  - With ATRA may replace standard ATRA + chemo
- Can chemotherapy be minimized or eliminated? Is ara-C needed? High-risk only?
  - Need only for high-risk (if no ATO)

Single Agent Arsenic in Untreated APL



Mathews, Blood 2006; 107: 2627 – 2632.

Long Term Follow-Up: ATO Single Agent

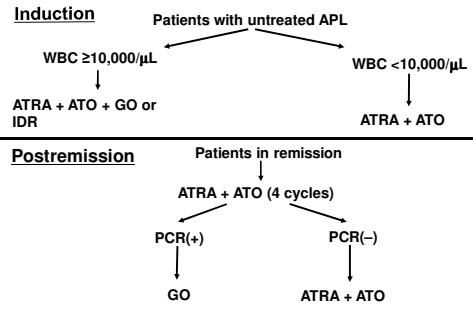


Good Risk Group Relapses = 2
(both prolonged CR after salvage and auto: 100% OS)

High Risk Group Relapses = 11

Mathews Blood, 2006 and update from 5th International APL Symposium Rome, 2009; Blood 2009 (abstr 846)

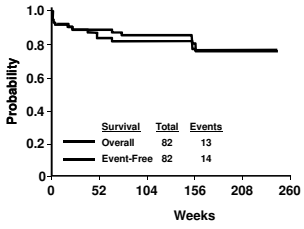
ATRA + Arsenic in Untreated APL



Rivandi, J Clin Oncol, 2008; 27(4):504-10

ATRA + Arsenic in Untreated APL

Pts in CR	90%
Low risk	95%
High risk	81%
Median days to CR	29
Pts in Molec CR	97%
Relapse	
Low risk	0
High risk	12%



Rivandi, J Clin Oncol, 2008; 27(4):504-10

New Agents To Watch

Agent	Mechanism	Comments
XIAP antisense oligo	Apoptosis inhibitor of caspases 3/9	Effective w/chemo as early reinduction
CPX-351	Liposomal fixed molar ratio of dauno/ara-C	Phase II rando trial underway
Amonafide	Topo II inhibitor	Phase III trial underway
Sorafenib/AC220	Multikinase inhibitor	CRs as single agents

Schimmer J Clin Oncol, 2009; Bayne J Pharm Sci, 2008; Burcu Leukemia, 2008; Metzelder Blood, 2009, 113: 6567 - 6571; Cortes Blood, 2009 (abstr 636)

Induction in AML

- Daunorubicin (or ida) + ara-C remain standard
- Gemtuzumab may be beneficial in fav/intermediate-risk, but not yet outside a trial
- Dauno 45 mg dose no longer standard; give at least 60-90 mg dose (for fav- and intermed-risk)
- Clofarabine promising for older adults
- *FLT3* inhibitor trials underway +/- chemo, but not yet outside a trial

New Postremission Strategies

Postremission Chemotherapy
General Comments

- Dose response effect with ara-C among younger pts, but no evidence consol benefits older pts
- Repetitive courses of HiDAC may be better than single course, but not clear
- Repetitive courses of non-HiDAC regimens appear as good as HiDAC, but multi-agent consol not better than HiDAC
- CBF leukemias appear particularly sensitive to repetitive courses of HiDAC or other intensive chemotherapy
- No role for maint except APL

Cassileth N Engl J Med, 1998; Grimwade Blood, 1998; Moore Blood, 2005; Appelbaum Br J Haematol, 2006

Gemtuzumab Ozogamicin (GO) In Induction: MRC AML15

Induction	Consolidation
DA ± GO vs ADE ± GO vs FLAG-Ida ± GO	→ MACE-MiDAC ± GO vs HiDAC ± GO (3.0 vs 1.5 mg/m^2)

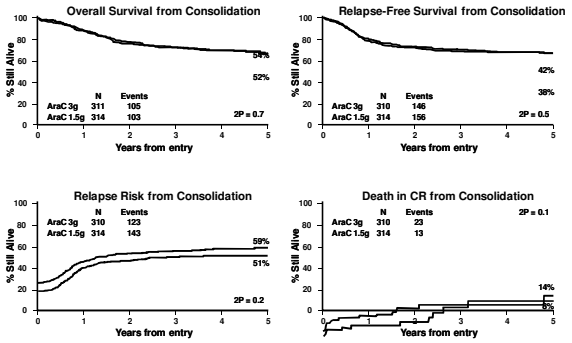
Burnett Blood, 2006 (abstr 13)

MRC AML15: Post-induction Outcomes

	5-yr death in CR	5-yr relapse rate	5-yr RFS	5-yr OS
Ara-C	10%	53%	42%	54%
MRC	15%	51%	42%	52%
Ara-C 1.5 gm	9%	58%	38%	54%
Ara-C 3 gm	14%	51%	43%	52%
5 courses	0%	58%	42%	60%
4 courses	1%	53%	46%	58%

Burnett ASH 2009 (abstr 484)

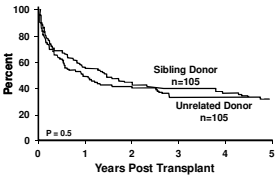
AML 15: Ara-C dose



Burnett Blood 2009 (abstr 484)

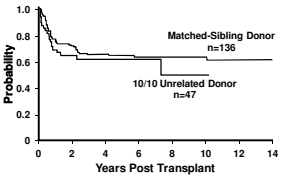
Equivalent Outcome of MUD and MSD Allogeneic HSCT in AML

Survival Following Transplantation For AML in CR1 (n=18)/>CR1 (n=87)



Moore, BBMT, 2007; 13(5):601-7

Survival Following Transplantation For AML in CR1



Pagel, Blood, 2007 (abstr 330)

Reduced-Intensity Conditioning HCT in High-Risk AML and MDS

Study	N	Med age	ED %	DFS %	OS %
Tauro	76	52	9	37	42
Hegenbart	122	58	2	44	48
Oran	112	55	7	NR	44
Valcarel	93	53	8	43	45

Indications For Allogeneic Transplant in Young Patients with AML in CR1

Cyto/Molec Genetic Risk	HLA-Matched Sib	MUD/UC
Fav, all except	No	No
c-KIT	Yes	Yes
Intermed, all except	Yes	Possibly
FLT3-/NPM1+/TET2-	Possibly	No
Unfavorable	Yes	Yes

What's New That Changes Practice?

- ***NPM1*** **and** ***FLT3*** **gene mutations should be searched for in NK AML,** ***c-KIT*** **in CBF**
- **Dauno 60-90 mg dose appropriate**
- **Ara-C 1.5 gm dose appears as good as 3 gm dose as consol for AML in CR1; 1 cycle may be as good as 3-4**
- **If** ***NPM1+/FLT3-/TET2-*****, may not benefit from allogeneic HCT, altho no prospective trial confirms**

What's New That Changes Practice?

- **In CBF AML, if** ***c-KIT+,*** **consider allogeneic HCT, but data based on few patients**
- **Consider MUD for any patient considered for MSD allogeneic HCT**
- **Treatment of choice for unfavorable cytogenetics is MUD if no MSD available**
- **RIC HCT for older adults**

Current Therapeutic Strategies in AML-2009

- **Induction: dauno 60-90 mg/m2/d x 3d (or ida) + ara-C 100 mg/m2/d x 7d c.i. (novel agents in older adults if not fit)**
- **Consol: multiple cycles (1-4) of high- or intermed-dose ara-C or equivalent in younger pts, particularly CBF; no clear role in older adults (can give 1 cycle at 1-1.5 gm/m^2)**
- **Allogeneic HCT for intermed- and high-risk (consider alternative donor for high-risk if no sib); consider in CBF with *c-KIT*; not if *FLT3-NPM1+/TET2-*; RIC for older adults**
- **Autologous HCT continues to be studied**
- **No maintenance (except ? APL and high-risk)**

Paschka J Clin Oncol, 2006; Schlenk N Engl J Med, 2008

Acknowledgments

ECOG Leukemia Committee

North American Leukemia Intergroup

European LeukemiaNet Colleagues