AML
Update on Diagnosis and Treatment

someday is today | LEUKEMIA & LYMPHOMA SOCIETY® fighting blood cancers

Welcome and Introductions

AML
Update on Diagnosis and Treatment

someday is today | LEUKEMIA & LYMPHOMA SOCIETY® fighting blood cancers

Elihu H. Estey, MD

October 31, 2013

Topics

- What is AML?
- Treatment-related mortality (TRM) vs. resistance as causes of treatment failure
- Standard therapy vs. investigational therapy
- Transplant
- Making patients' lives more pleasant

Typical Case

- Patient has fatigue, shortness of breath
- Blood count shows anemia, which causes symptoms
- Platelet count, neutrophil count also low possibly leading to bruising (platelets) or infection (neutrophils)
- Bone marrow obtained: site of blood cell formation

What is AML?

- RBCs, PMNs, platelets limited life span
- Mechanism to replace them resides in marrow:
  immature cells ("blasts") ➔ mature RBC, PMN, plts
- In AML some normal blasts ➔ abnormal
  - don't mature, accumulate (marrow failure)
  - prevent normal blasts from maturing (marrow failure)
  - escape into blood
- Bone marrow failure ➔ infections, less often bleeding
- Diagnosis: accumulation of blasts in marrow, blasts in blood

Principles of Treatment

- Reduction in abnormal blasts allows normal blasts to mature ➔ remission
- CR : > 100 plts, > 1000 PMN, marrow < 5% blasts
- CR: probably necessary for cure
- But must continue for > 3 years w/o relapse
- After CR > 3 years probability relapse 5%
- Major problem: distinguishing abnormal from normal cells: goal of "targeted therapy"

Reasons for Treatment Failure

- Treatment–related mortality (TRM)
- Resistance to treatment:
  - no remission despite no TRM
  - relapse

"Less Intense" Rx

- Putative advantages
  - less toxic (often emphasized)
  - more effective
- Fundamental point: lack of efficacy is major problem in AML therapy

TRM vs. Resistance as Cause of Failure With 3+7

	Age		
	56-65	66-75	>75
Pts	246	274	80
CR	46%	39%	33%
TRD (d30)	11%	20%	31%
Resis	**43%**	**41%**	**36%**

Appelbaum et al. Blood 2006;107:3481-3485

Relapse vs. Death in CR

Age	PS at CR	Pts.	Rate of Relapse	Die in CR	Ratio
< 60	<2	428	25.9	1.7	15.2
< 60	2-4	54	22.3	4.6	4.8
≥ 60	<2	262	46.0	10.8	4.3
≥ 60	2-4	120	51.7	17.2	3.0
≥ 70	2-4	71	67.3	22.0	3.1

Yanada et al. Haematologica 2008;93:633-34

Effect of Time (1991-2009) on TRM

- SWOG
  - 1,409 patients
  - 55% 3+7 (Dnr 45 then 60)
  - 19% 3+7 + GO
  - 14% ME
  - 12% Dnr + HiDAC
- MDA
  - 1,942 patients
  - 92% HiDAC-containing regimen

TRM Summary

Cohort	91-95	96-00	01-05	06-09	P-value
SWOG	18%	13%	12%	3%	<0.001
MDA	16%	14%	9%	4%	<0.001

Decline in TRM with Time

- TRM rates decreased over time
- Pt. characteristics more favorable over time
- Results same after accounting for this
- Same is true in younger & older patients (selection bias less likely an issue)
- Major issue is efficacy, not toxicity

Othus et al. Leukemia epub 6/13/13 doi: 10.1038/leu.2013.176

Management Options for AML

- Supportive care only
- Standard therapy
- Clinical trial

Supportive Care Only

- Life expectancy probably better than originally described (1961)
- But must be viewed relative to 20-25 year life expectancy for healthy patients aged 60-70
- Morbidities: frequent transfusions and doctor visits; fatigue

Standard Therapy vs. Clinical Trial

- Standard → given to so many patients that results not in doubt, examples 3+7, decitabine, azacitidine
- Trial → results largely unknown
  - preclinical rationale imperfect
  - small number patients treated
  - patients differ (age, cytogenetics, etc.)
  - short follow-up
- So deciding standard vs. trial depends on how patient views results standard

Prognostic Factors With Standard Therapy: TRM

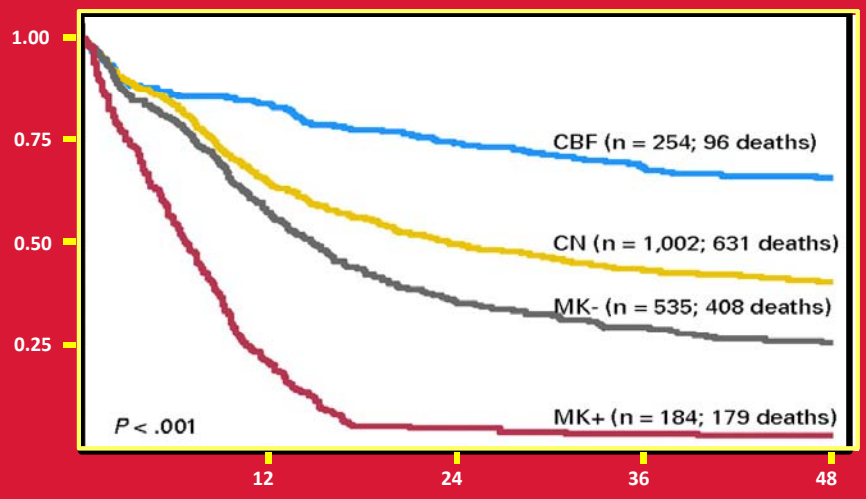
- Performance status
- Co-morbidities
- Organ function
- Age

Example 1: otherwise healthy 50 y.o. TRM <3%
Example 2: debilitated with abnormal kidney function 75 y.o. TRM >50%
THINK BEYOND AGE!!!!!!

Prognostic Factors with Standard Therapy: Resistance

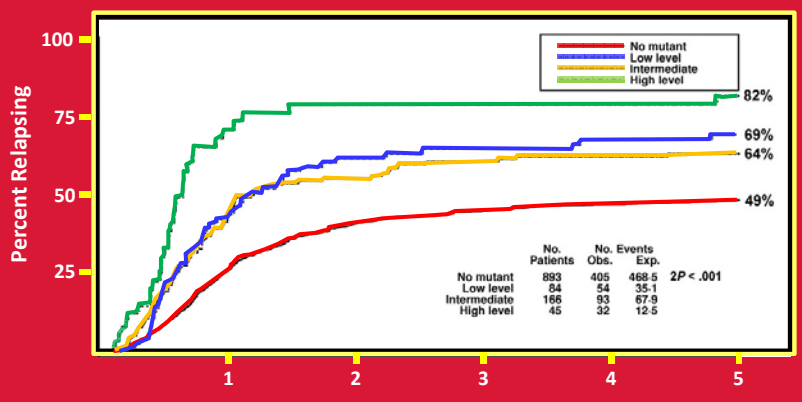
- Cytogenetics in AML blasts
  - best: inv(16) and t(8;21)
  - average: normal (NK)
  - below average: others, not MK
  - MK
- Various mutations in patients with NK
- Secondary AML
  - after chemotherapy for breast, lymphoma, etc.
  - after MDS or other hematologic disorders
- Age

Effect of Monosomal Karyotype on Survival



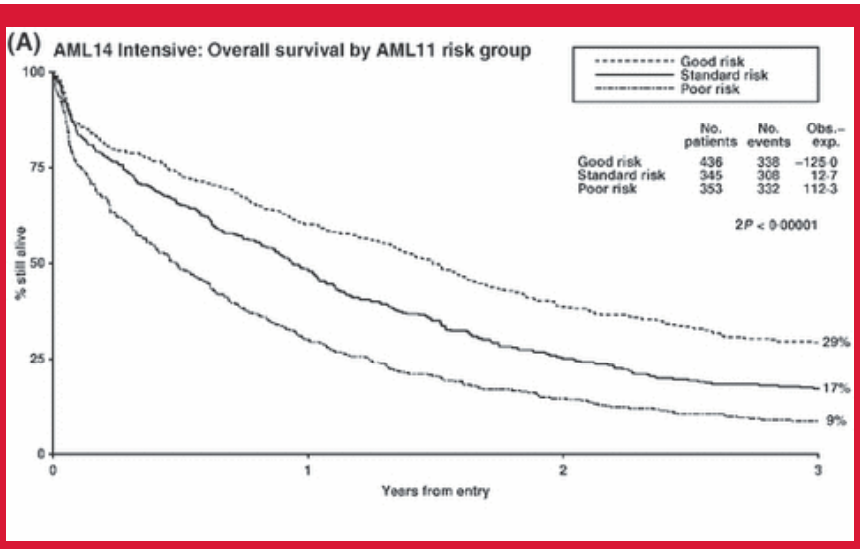
Breems D A et al. JCO 2008;26:4791-4797

Outcome According to FLT3/ITD Expression Level

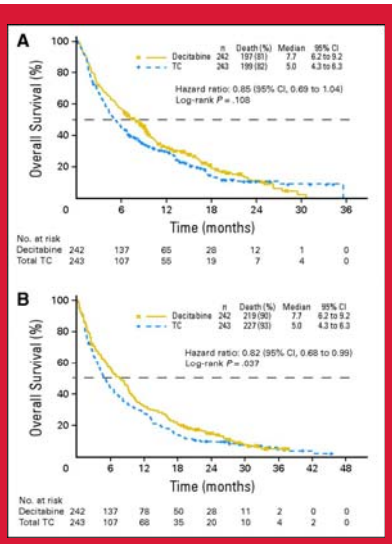


Gale et al. Blood 2008;111:2776-84

AML14 Intensive: Overall Survival by AML11 Risk Group



(A) Overall Survival (Kaplan-Meier Method) in a Protocol-specified 2009 Clinical Cut-off Analysis of Decitabine and Treatment Choice (TC) in the Intent-to-treat Population



JOURNAL OF CLINICAL ONCOLOGY ASCO

Medical Significance Azacitidine Trial

- If healthy, 70 year old might expect to live 15 years (180 months)
- With LDAC most likely lives 16 mo. Retaining 9% of life expectancy (16/180)
- With aza most likely lives 24 mo., retaining 13%
- Need better means to depart from average prediction

Trial vs. Standard

- Reason to go on trial: dissatisfaction with result with standard!
- Same information can lead to different decisions in different patients
- Results with standard are often not discussed with patient: don't ask, don't tell

Which Trial?

- Clinicaltrials.gov → 33 trials for pts. age > 65
- Implies no one certain which best
- Reasons for uncertainty
  - imperfect understanding of difference between AML blast & normal counterpart
  - insufficient # pts. treated
  - patients differ among themselves
  - short follow-up

Which Trial?

- Trial offered depends where you go
- Cannot recommend internet search to intellectualize best trial
- Go on trial in academic center where you are most comfortable
- Make sure trial has stopping rules!
- Be prepared for success: many currently curable diseases once had same prognosis as AML until trials done (AIDS, CML, APL)

"Targeted Therapy"

- Selectively affects AML blast
- But several targets may need to be affected simultaneously (example imatinib)
- Eventually combined with chemotherapy (gemtuzumab ozogamicin, FLT3 inhibitors)
- Boost immunologic response

Allogeneic Hematopoietic Cell Transplant (HCT) in CR1

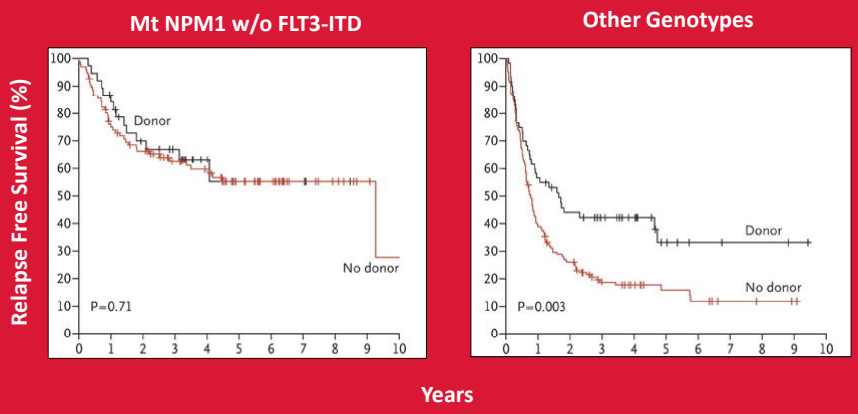
Cyto	Donor	No Donor	HR (95% CI)
Best	188	359	1.07 (0.83-1.38)
Inter	864	1635	0.83 (0.74-0.93)
Worst	226	366	0.73 (0.59-0.90)

Cyto as per ECOG/SWOG

HR < 1.0 means longer survival with HCT

Koreth et al. JAMA 2009;301:2349-61

Relapse-free Survival in CR1 According to Availability of HLA-Matched Sibling



Schlenk RF et al. N Engl J Med 2008;358:1909-1918.

Extensions of HCT Beyond Ablative Sib in CR1

- Reduced intensity HCT up to age 75-relies on graft vs. AML effect
- Matched unrelated reduced intensity HCT up to age 75
- Cord blood
- Haploidentical donors
- HCT survival better 2003-07 vs. 1993-97

Future

- Merging of HCT & chemotherapy
- To eliminate minimal residual disease pre-HCT
- To prevent relapse post HCT
  - azacitidine
  - FLT3 inhibitors
  - T cell therapies: GVL w/o GVH

Making Patients' Lives Easier

- Discharge once chemotherapy completed
- Discharge once fever gone regardless neutrophil count
- Eliminating "neutropenic diet"

AML
Update on Diagnosis and Treatment

someday is today | LEUKEMIA & LYMPHOMA SOCIETY® fighting blood cancers

Question & Answer Session

The speaker's slides are available for download at www.LLS.org/programs

AML
Update on Diagnosis and Treatment

someday is today | LEUKEMIA & LYMPHOMA SOCIETY® fighting blood cancers

For more information about AML and other programs from The Leukemia & Lymphoma Society (LLS), please contact an LLS Information Specialist:

TOLL-FREE PHONE: (800) 955-4572

EMAIL: infocenter@LLS.org

LIVE ONLINE CHAT: www.LLS.org/informationspecialists