

Use of Transplantation for the Treatment of Patients with Leukemia

Robert S. Negrin, MD
Professor of Medicine
Chief, Division of Blood and Marrow Transplantation
Stanford University

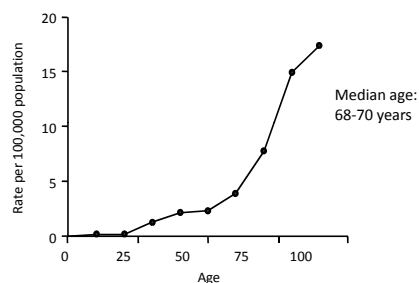
Goals of Presentation

- Discuss classification and risk stratification for AML and ALL
- Describe the role of transplantation for AML and ALL
- Highlight important management issues

Acute Myelogenous Leukemia

- U.S. leukemia incidence = 27,000; annual deaths = 18,000
- AML accounts for ~80% of all acute leukemia in adults
- Complete Remissions (CR) achieved in ~70% with chemotherapy
- Prognostic factors include cytogenetics and molecular abnormalities
- Overall cure rate with standard chemotherapy ~30-50% for younger adults; <10% for patients > age 60

Age-related Incidence of AML

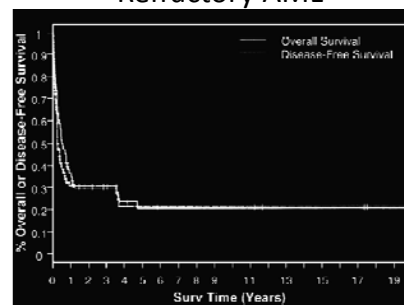


Adapted from Wingo PA, et al. *CA Cancer J Clin.* 1995;45:8-30.

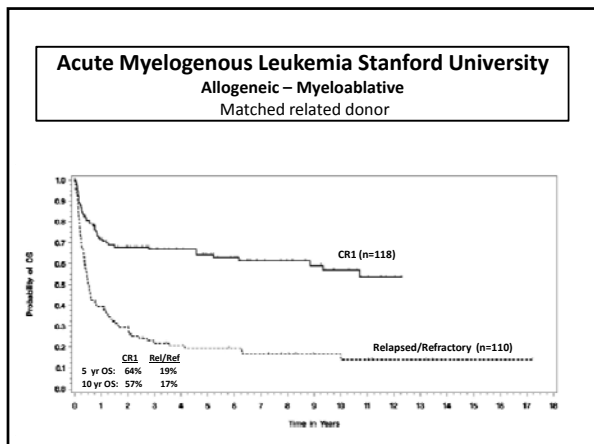
Indications for Allogeneic Transplantation

- Induction failure
- CR1
- Beyond CR1

Allogeneic HCT for Primary Refractory AML



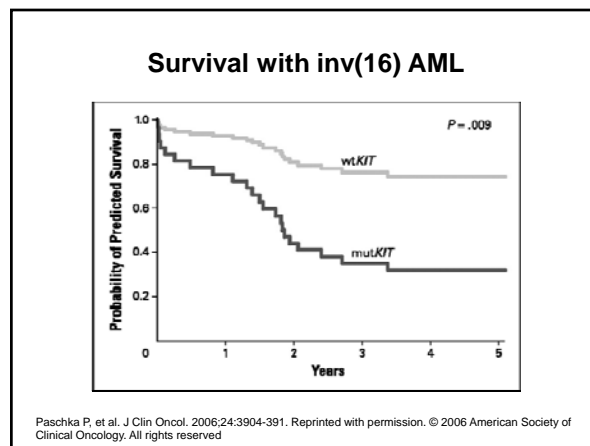
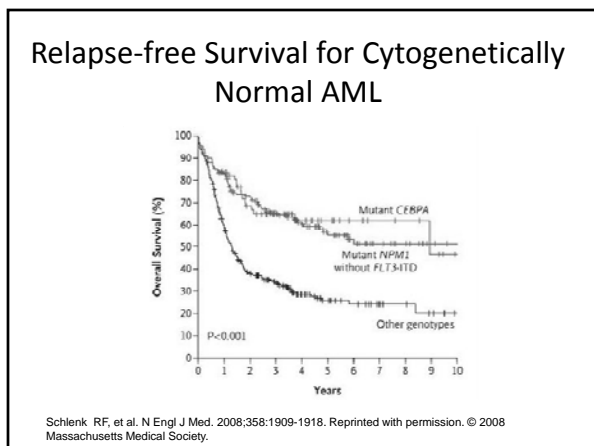
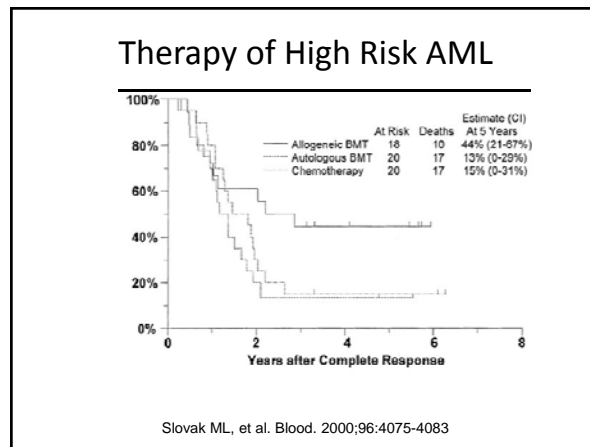
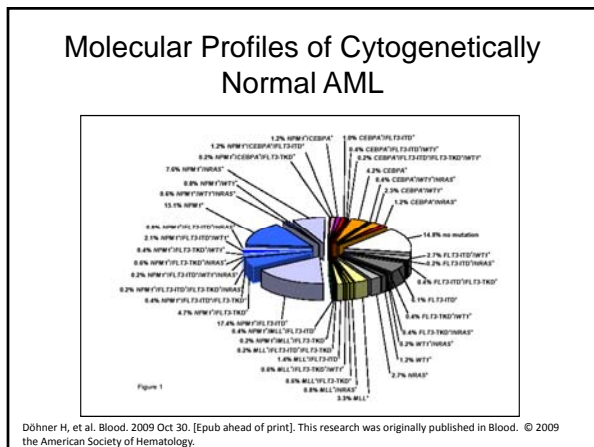
Fung HC, et al. *Biol Blood Marrow Transplant.* 2003;9:766-770. Reproduced with permission.

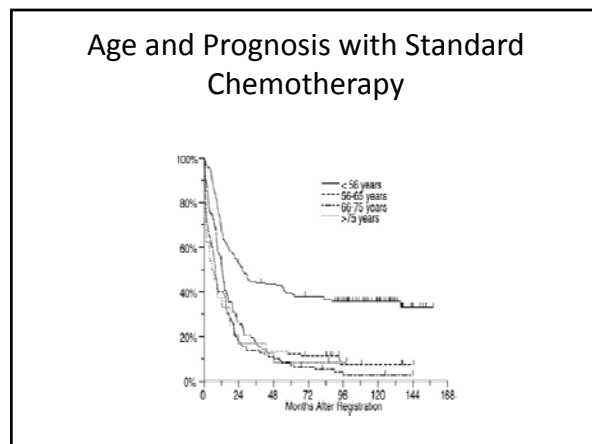
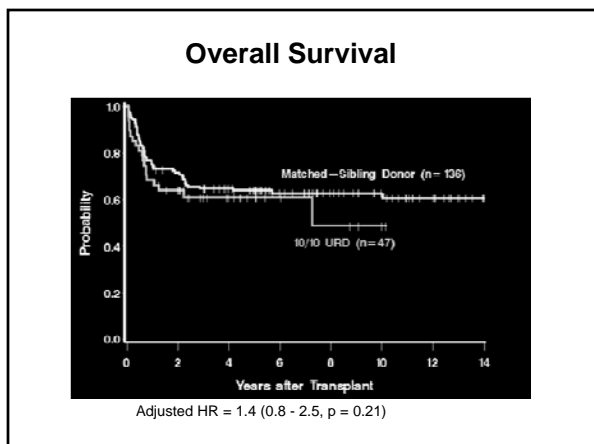
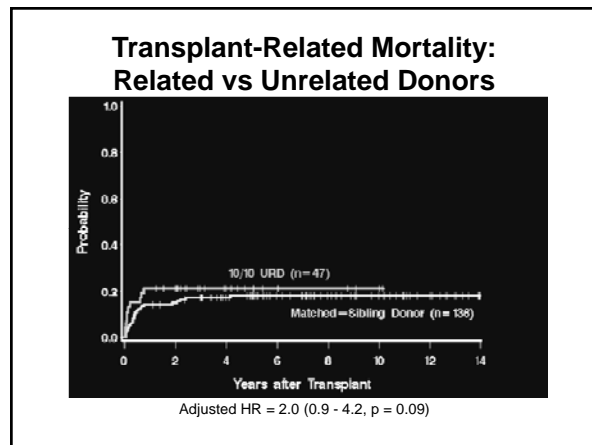
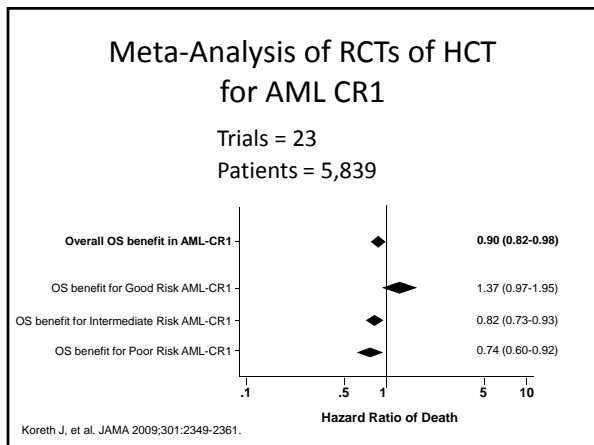
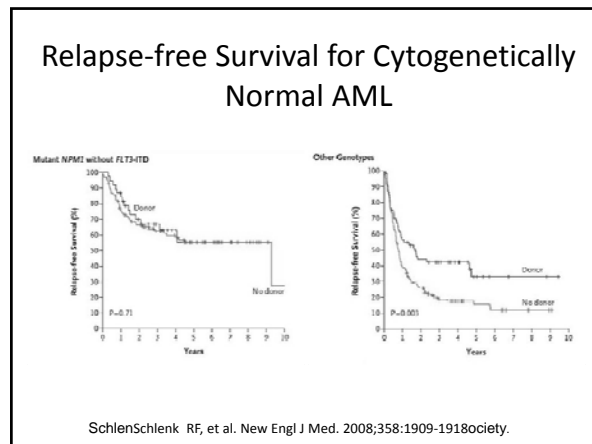
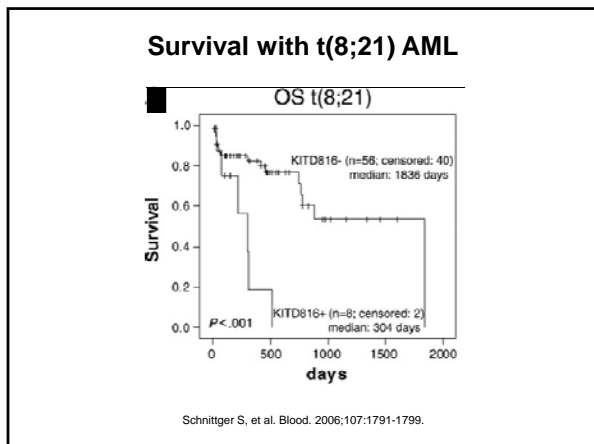


NCCN

RISK STATUS BASED ON CYTOGENETICS AND MOLECULAR MUTATIONS

RISK STATUS	CYTOGENETICS	MOLECULAR MUTATIONS
Better-risk	inv(16) [†] t(8;21) [†] t(16;16) [†]	Normal cytogenetics with isolated NPM mutation
Intermediate-risk	Normal +8 only (9;11) Other abnormalities not listed with better-risk and poor-risk cytogenetics and molecular mutations	c-KIT [†] in patients with t(9;21) or inv(16)
Poor-risk	Complex (> 3 abnormalities) -5 -7 6q- 2q- Abnormalities of 11q23, excluding t(9;11) inversion 3 t(3;3) t(6;9) t(9;22) [†]	Normal cytogenetics with isolated FLT3 mutations

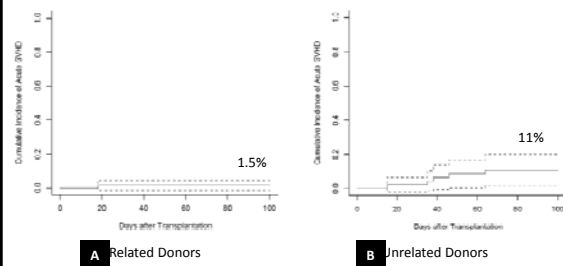




TLI/ATG Reduced Intensity Conditioning

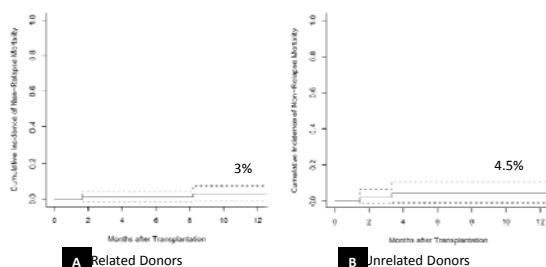
- Animal studies have demonstrated that novel conditioning with TLI/ATS results in protection from GVHD
 - Pillai et al. J Immunol 178:6241, 2007
 - Pillai et al. Blood 113:4458, 2009
- Translation to the clinic demonstrating low acute GVHD incidence and severity and low TRM
 - Lowsky et al. N. Engl. J Med 353:1321, 2005
 - Kohrt et al. Blood 114:1099, 2009

Low Incidence of Acute GVHD



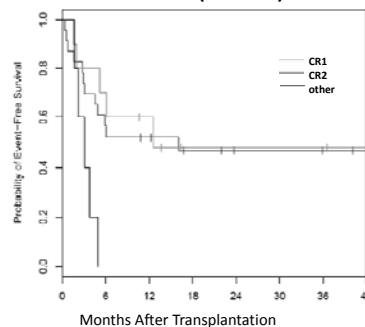
Kohrt et al. Blood 2009

Low Non-Relapse Mortality

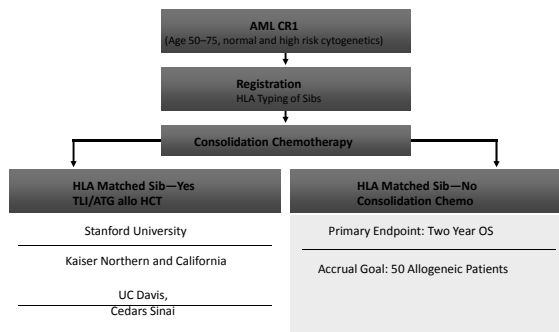


Kohrt et al. Blood 2009

Event-Free Survival Among AML Patients (N=47)



California AML Trial



Acute Lymphocytic Leukemia (ALL): Epidemiology

- 3830 new cases in the US annually
- Accounts for ~20% of adults with acute leukemia
 - 60% of ALL patients younger than 20 years of age; most common malignant disease in children
 - 30% of all childhood cancers
 - More common in males: 62%
- Greatest incidence in the US among Hispanics
 - Higher incidence in whites vs blacks

Jemal A, et al. CA Cancer. 2004;54:8-29.

Age-Specific Annual Incidence of ALL (SEER Data: 1998-2002)

- Peak incidence in childhood, followed by sharp decline in early adolescence
 - Increase in incidence during older decades

Select Age Group, Yrs	Incidence
– 4	> 7 per 100,000
5-9	3-4 per 100,000
15-19	1-2 per 100,000
25-50	0.4-0.6 per 100,000
> 60	0.9-1.6 per 100,000

Larson MD. Acute lymphoblastic leukemia: older patients and newer drugs. ASH Education Book; 2005.

Acute Lymphoblastic Leukemia Outcome

- High remission rates possible in adults and children
- Leukemia-free survival in children 2-10 years of age: 80%
 - Most adults experience relapse

	Complete Remission	Leukemia-Free Survival
Adults	80% to 90%	35%
Children (2-10 yrs of age)	97%	80%

Pui CH, et al. N Engl J Med. 2006;354:166-178.

Prognostic Indicators

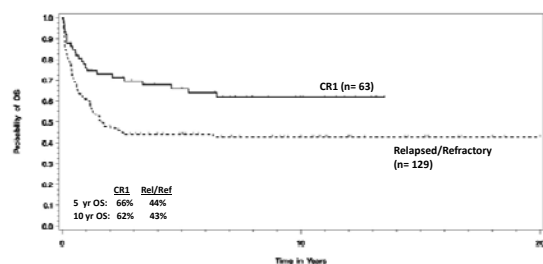
- Standard risk
 - Decreasing age (continuous variable; < 35 years)
 - Decreasing WBC (continuous variable)
 - < 30,000 for B-cell lineage
 - < 100,000 for T-cell lineage
 - T-cell lineage
 - CR within 4 weeks
- Coexpression of myeloid markers: no prognostic impact
- Chromosomal and molecular changes

Stem Cell Transplantation (SCT): CIMBTR Recommendations

- First CR
 - Allo SCT or MUD in high-risk patients
 - Role in standard-risk patients less clear but may result in superior outcomes
 - Auto SCT: no benefit over chemotherapy
- Second CR
 - Allo SCT recommended either in CR2 or at first relapse

Hahn T, et al. Biol Blood Marrow Transplant. 2006;12:1-30.

Acute Lymphoblastic Leukemia Stanford University Allogeneic - Myeloablative Matched related donor



ALL: SCT at First CR

Study	Endpoint	CHT	Auto SCT	Allo SCT	Improved Outcome
CIBMTR vs German studies	LFS	32%	--	34%	NS
JALSG 93	OS	40%	--	46%	NS
LALA 87	OS	35%		48%	NS
LALA 87 SR	OS	45%		51%	NS
LALA 87 HR	OS	20%		44%	Allo
LALA 94 HR	OS	35%	44%	51%	Allo
GOELAL02 HR	OS	--	40%	75%	Allo

Molecular and Cytogenetic Subtypes of B-Lineage ALL

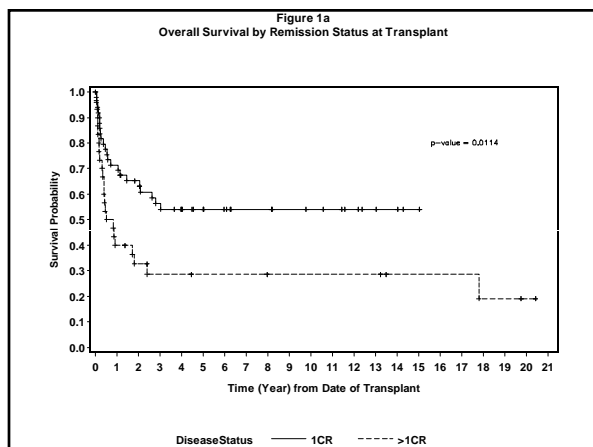
Subtype (Favorable Cytogenetics)	Karyotype	Childhood Frequency, %	Adult Frequency, %	Childhood EFS, %	Adult EFS, %
Hyperdiploidy	> 50 chr	25	5	80-90	40-50
<i>TEL/AML1</i>	t(12;21)	25	3	85-90	?
<i>MYC</i>	t(8;14)	2	5	75-85	60-70
<i>bcr/abl</i>	t(9;22)	5	33	20-40	< 10
<i>MLL/AF4*</i>	t(4;11)	3	6	30	15

*Most common in infant leukemia (mixed AML-ALL).

Bassan R, et al. Crit Rev Oncol Hematol. 2004;50:223-261.

Philadelphia Chromosome (Ph+) ALL

- t(9;22) *bcr/abl* translocation
- Precursor B cell
- Incidence continuously increasing with age
 - Rare in children; 50% incidence in ALL patients older than 55 years of age
- Associated with very poor outcome
 - No cure with intensive ALL chemotherapy (all ages)
 - Cure with SCT
 - Lower cure rate than other ALL subtypes



Conclusions

- Role of allogeneic transplantation for patients with acute leukemia clearer than ever before due to prognostic factors
- CR1 for higher risk patients
- >CR1 for all patients
- Identification of donor early in the course of therapy a must