ASH/FDA Workshop on Clinical Endpoints in Acute Leukemia

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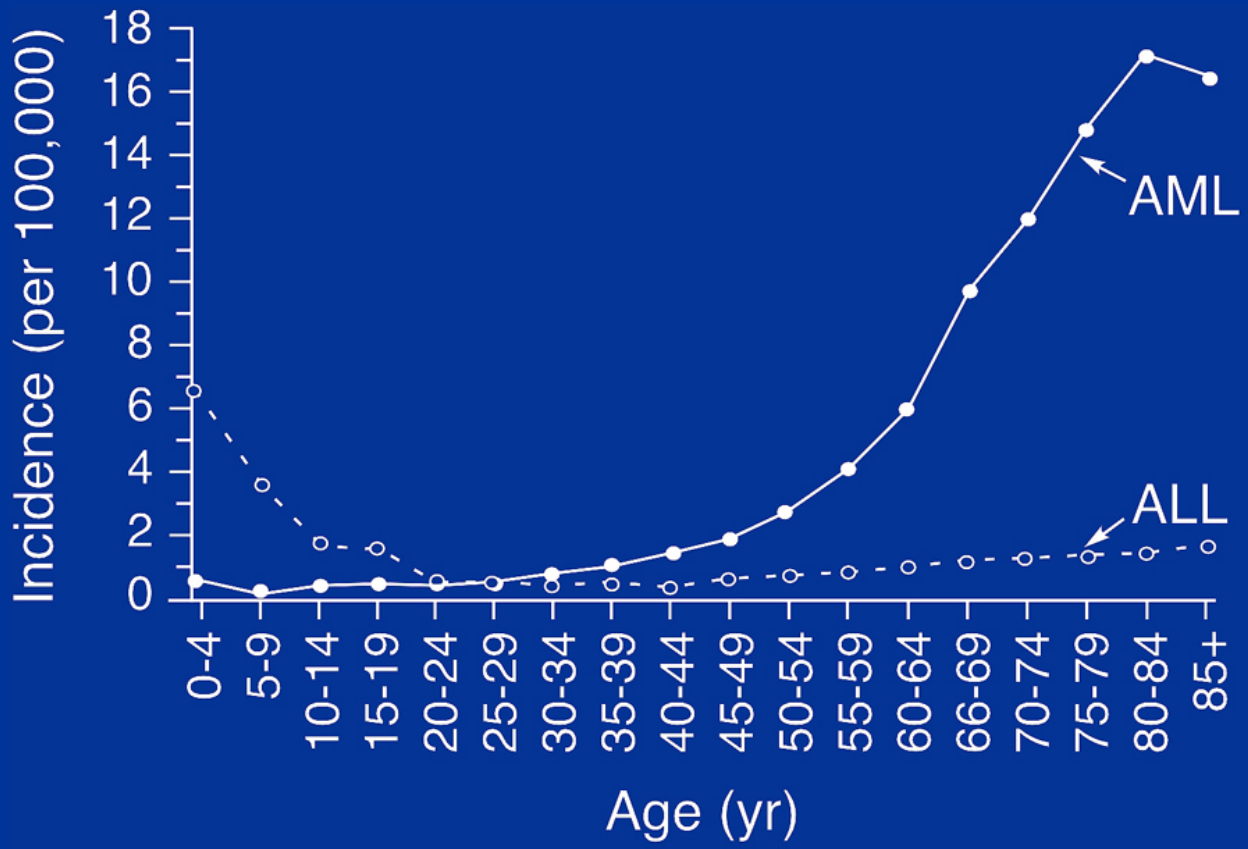
Heterogeneity of Patients and Their Disease

I. Patient heterogeneity
   - A. Age
   - B. Performance status

II. Disease heterogeneity
   - A. AML in older patients
   - B. AML in younger patients
   - C. Adult ALL
   - D. Pediatric ALL

III. Conclusions

Age-related Incidence of AML and ALL



Performance Status and Age in AML

N = 437

Age	Performance Status			
	0	1	2	3
56-60	.28	.49	.11	.08
61-65	.27	.42	.17	.12
66-70	.26	.48	.19	.13
71-75	.23	.49	.16	.11
76+	.16	.47	.18	.18

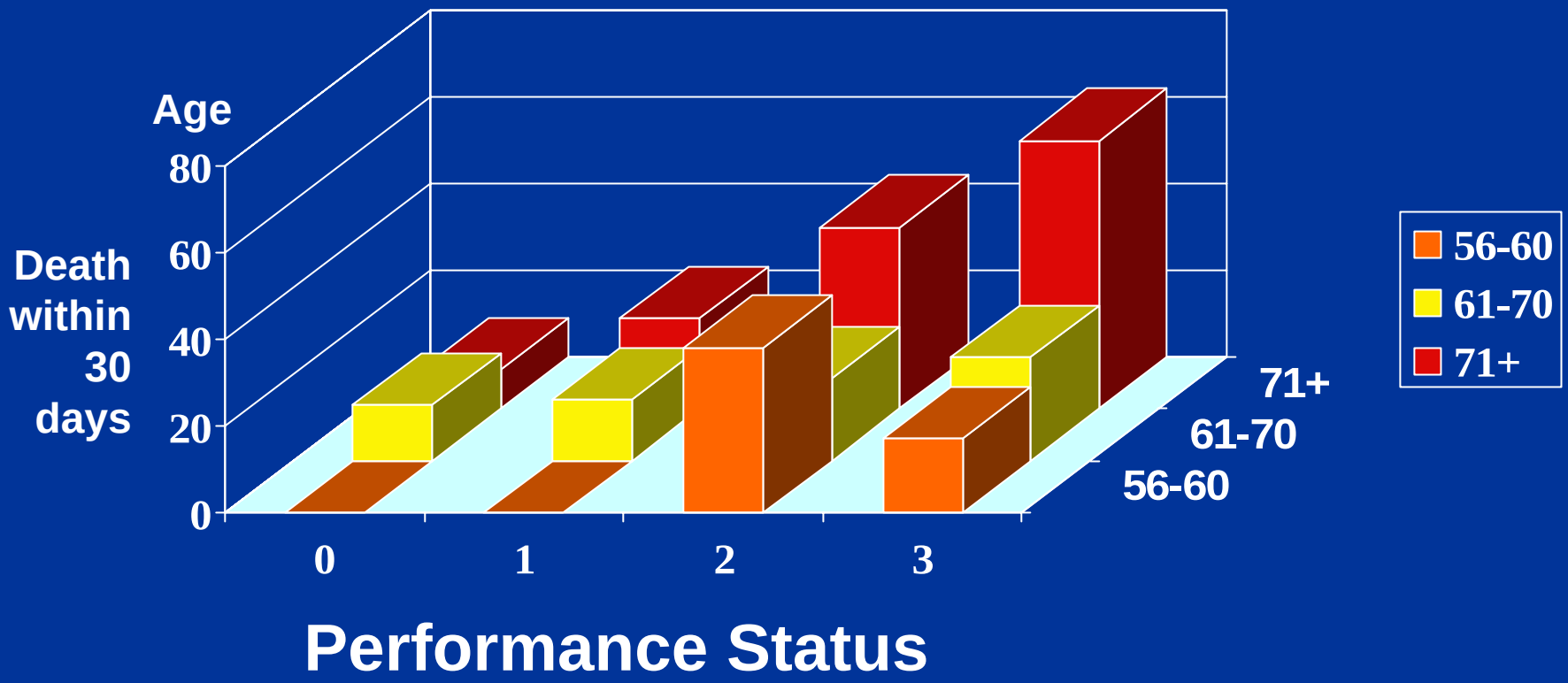
Age, Performance Status and Early Death in AML

N = 437

Performance Status	Death within 30 days		
	56-60	61-70	71+
0	0%	13%	9%
1	0%	14%	21%
2	38%	19%	42%
3	17%	24%	62%

Age, Performance Status and Early Death in AML

N = 437



Performance Status and Co-morbidity

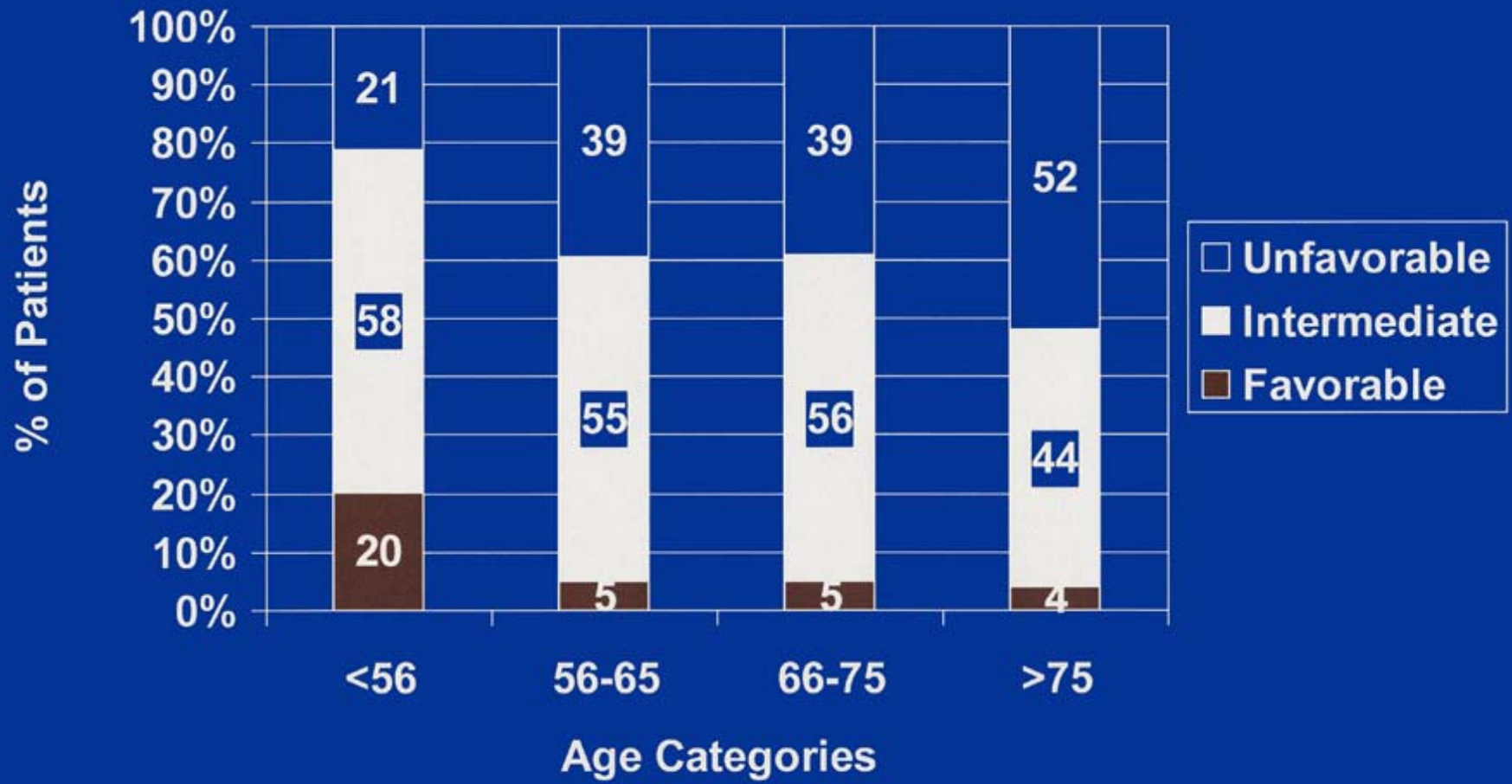
1. Reproducibility of performance status rating is variable
2. ECOG scale more reproducible than Karnofsky, but likely because ECOG has fewer categories (5 vs. 10)
3. Where it has been studied, little correlation between performance scores and co-morbidity scales

AML in Older Patients

1. More often preceded by myelodysplasia
2. Less proliferative
3. More frequently associated with unfavorable cytogenetics
4. Expresses multidrug resistance more often

Southwest Oncology Group Leukemia Committee

Percentage of Patients in Cytogenetic Risk Groups by Age Category



Cytogenetics by Age

	Age				
	< 56	56-65	66-75	> 75	p
-5 or 5q (%)	6	15	14	26	<.0001
-7 or 7q	8	19	18	22	<.0001
17p	2	9	7	11	=.0001
t(8;21)	7	4	2	0	=.0087
inv(16)	9	2	4	7	=.0011

Complete Response in Older AML Patients[1]

Feature	N	CR%	p (univariate)
AML onset			
2°	50	24	.0005
1°	161	52	
CD34 expression			
+	138	38	.0027
-	66	59	
MRK16			
Bright	102	34	.0019
Dim	33	45	
Negative	54	67	
Cytogenetics			
Unfavorable	52	21	< .0001
Other	112	55	
Functional Efflux			
Positive	101	35	.0039
Negative	74	58	

[1]Leith et al. Blood, 89:3323-3329, 1997

Factors Associated with Lower CR Rates in Older AML Patients (multivariate)[1]

N =211

Factor	p value
2°AML	.0035
Unfavorable cytogenetics	.0031
MDR1 expression	.0041

Patients with all three factors had a CR rate of 11% versus a CR rate of 81% in patients without all three.

[1]Leith et al., Blood 89: 3323-3329, 1997

MRC AML 11 (patients > 55)[1]

Induction – DAT vs. ADE vs. MAC
± G-CSF

Consolidation – 2 cycles vs. 6 cycles

[1]Goldstone et al., Blood 98: 1302, 2001

Factors Predictive of Outcome in Multivariate Analysis from MRC AML 11

Parameter	Endpoint	
	CR	OS
Cytogenetics	2×10^{-14}	8×10^{-11}
WBC	4×10^{-6}	6×10^{-13}
Age	2×10^{-5}	1×10^{-4}
2°	5×10^{-7}	1×10^{-6}
Performance status	3×10^{-4}	2×10^{-6}

Prognostic Factors in AML (Age < 56)

1. Cytogenetics
2. Age
3. WBC
4. 1° vs. 2° presentation
5. Response to cycle 1
6. MDR1 expression
7. FLT3 mutation

Factors Predictive of Survival in Multivariate Analysis from MRC AML 10 (age < 56)

Parameter	p value
Cytogenetics	2×10^{-16}
Response to cycle 1	$< 1 \times 10^{-30}$
Age	4×10^{-12}
WBC	0.002
1° vs. 2 °	0.04

Wheatley et al., BJH 107:69-79, 1999

Adult ALL – Adverse Risk Factors

Time to achieve CR	(>4 weeks)
Cytogenetic abnormalities	t(9;22), t(4;11)
White blood cell count	>25,000-35,000/mm^3
Age	>35
Immunophenotype	Pre-T CALLA-negative early pre-B
Mixed lineage	Myeloid antigen coexpression

Impact of Risk Factors in Adult ALL

No. of Adverse Features	Estimated 3-yr. Survival
0	91%
1	64%
2	49%
3	21%
4	0

Prognostic Factors in Childhood ALL

Factor	Favorable	Unfavorable
Age	> 1 and < 10 yr	< 1 or ≥ 10 yr
Sex	Female	Male
WBC	< 50	≥ 50
Immunophenotype	Common ALL	Pro B, T
Genetics	TEL/AML1, hyperdiploid	t(9;22), t(4;11), hypodiploid
Early response	< 5% blasts on d7 and d15	> 25% blasts on d7 or 15

Summary

- Within any general category of leukemia, there can be enormous heterogeneity in patient and disease characteristics that can have profound effects on treatment outcome.
- This observation must be taken into account in the design of any clinical trial attempting to assess the effectiveness of a given intervention.