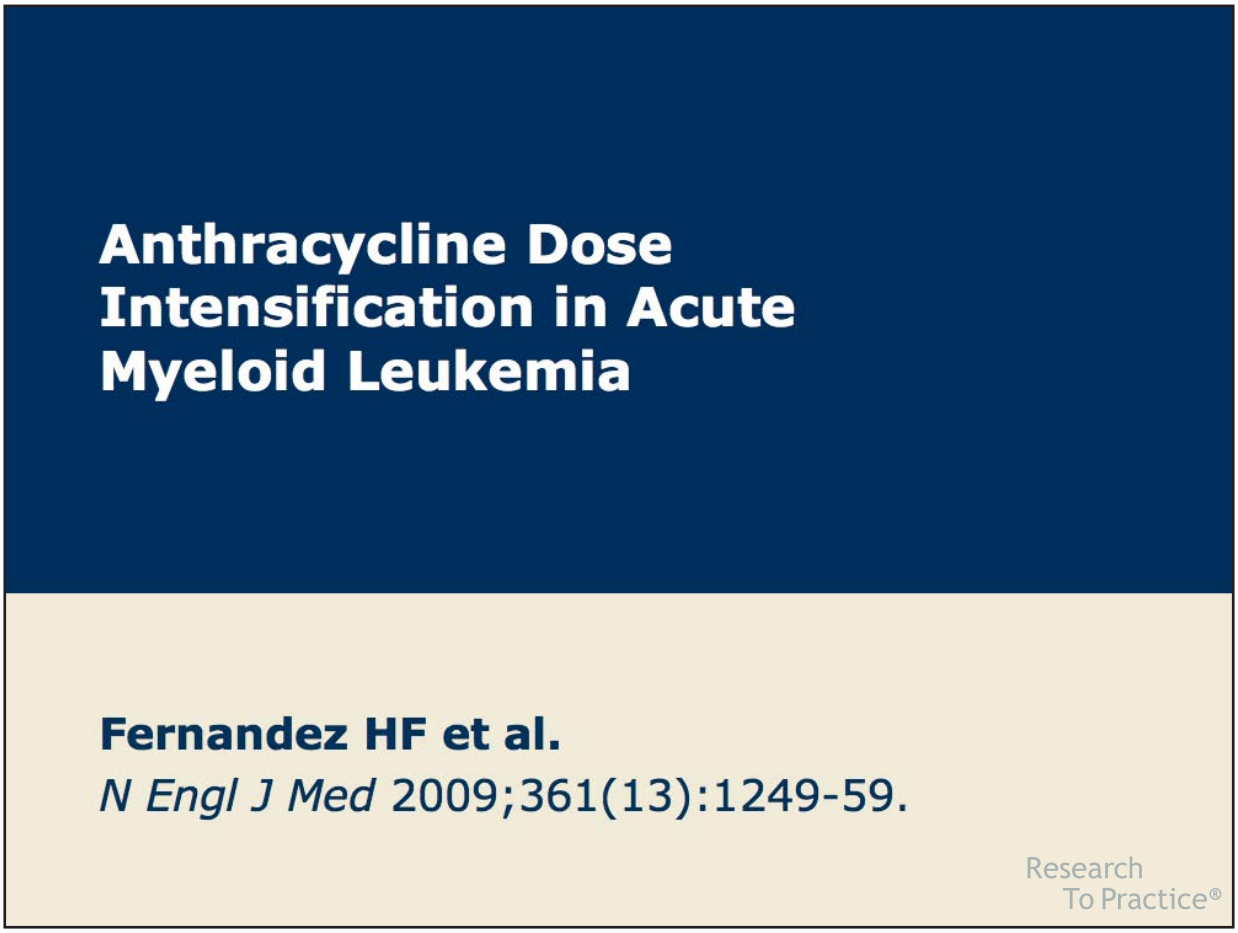
Anthracycline Dose Intensification in Acute Myeloid Leukemia (AML)

Presentation discussed in this issue:

Fernandez HF et al. **Anthracycline dose intensification in acute myeloid leukemia.** *N Engl J Med* 2009;361:1249-59. **Abstract**

Slides from the journal article



Introduction

- An anthracycline plus cytarabine is the usual induction therapy for patients with AML.
  - Daunorubicin (D) (45 mg/m^2/d x 3 days) plus cytarabine (C) (100 mg/m^2/d for 7 days) results in complete remission in 50-75% of patients.
- Neither the addition of other drugs to D/C, nor intensification of C has been shown to improve outcome.
- Studies with higher-dose D (70-95 mg/m^2/d x 3 days) are safe and improve rates of complete remission.

Objectives of the current study (ECOG-E1900):

- Assess whether high-dose, induction D (90 mg/m^2/d) improves survival compared to standard-dose D (45 mg/m^2/d) in patients under the age of 60 with AML.

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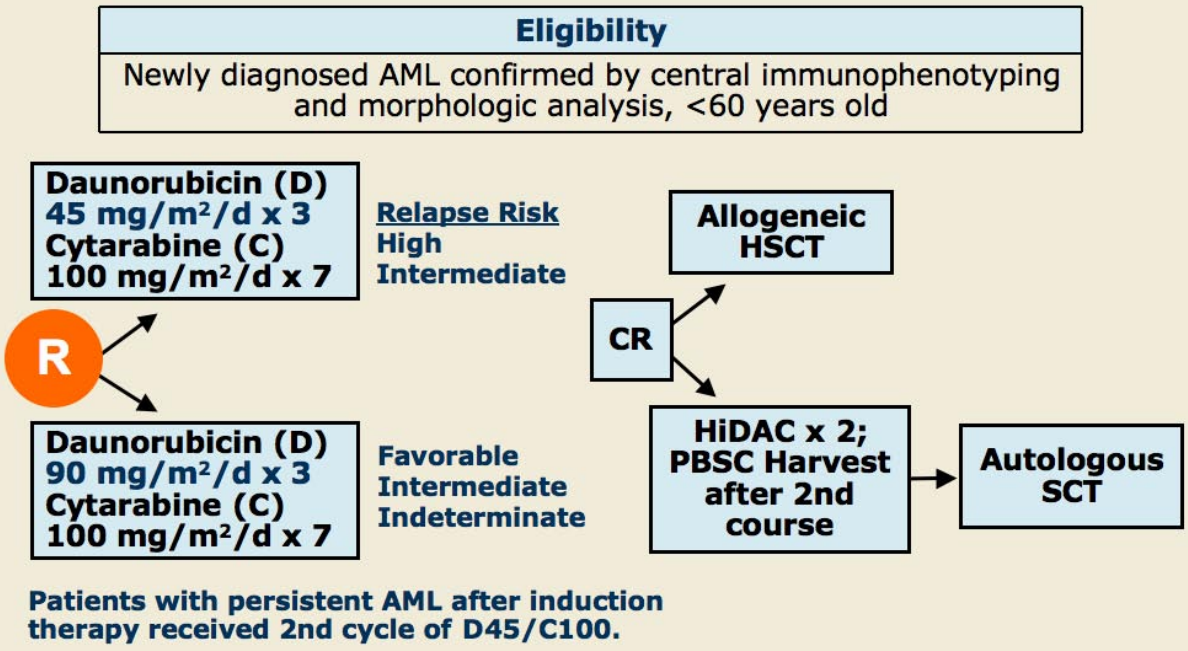
ECOG-E1900: Phase III, Randomized Study (N = 657)



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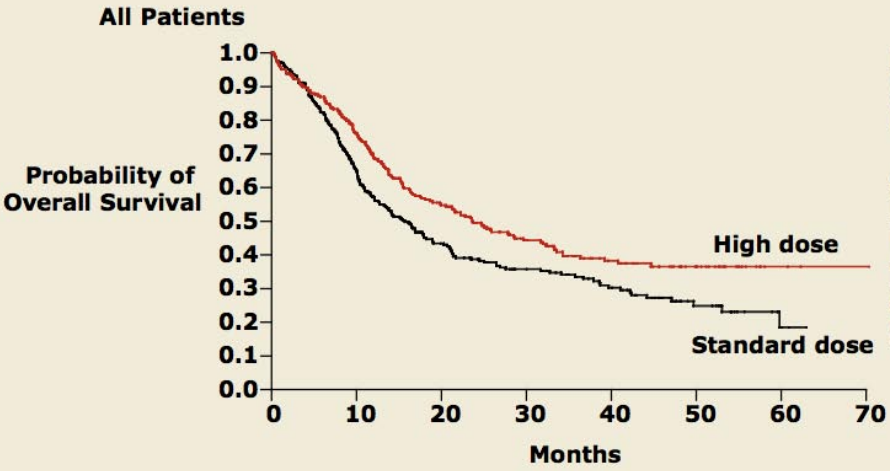
Overall Survival (Intent-to-Treat): All Patients



HR = 0.74
(95% CI, 0.60-0.92)
P=0.005

Adjusted for sex, age, Hemoglobin level, leukocyte counts, platelet counts and cytogenetic profile as continuous variables

Induction Treatment	Total	Deaths	Censored	Median Survival	
Standard dose (45 mg/m²/day)	330	199	131	15.7 mo	} p-value = 0.003
High dose (90 mg/m²/day)	327	168	159	23.7 mo	

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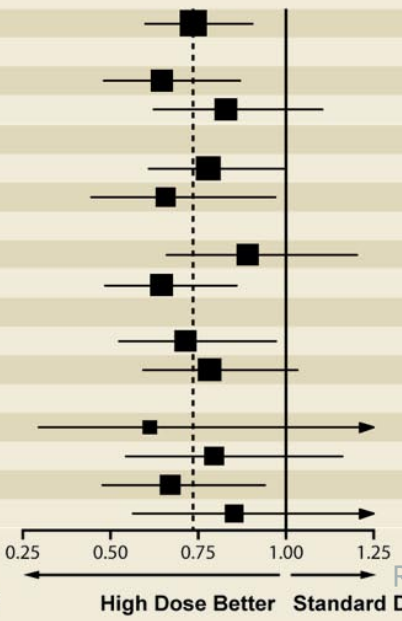
Hazard Ratios for Death According to Subgroup

Subgroup	Standard Dose (45 mg/m²/day) no. of events/total (%)	High Dose (90 mg/m²/day) no. of events/total (%)	Hazard Ratio	P Value
All patients	199/330 (60.3)	168/327 (51.4)	0.74	0.004
Age				
<50 yr	103/188 (54.8)	76/172 (44.2)	0.65	0.004
≥50 yr	96/142 (67.6)	92/155 (59.4)	0.83	0.20
Hemoglobin level				
<10 g/dl	136/229 (59.4)	123/233 (52.8)	0.78	0.05
≥10 g/dl	61/98 (62.2)	44/91 (48.4)	0.66	0.03
Platelet count				
<50,000/mm³	87/149 (58.4)	86/155 (55.5)	0.89	0.45
≥50,000/mm³	110/177 (62.1)	82/170 (48.2)	0.64	0.003
White-cell count				
<10,000/mm³	87/150 (58.0)	75/154 (48.7)	0.71	0.03
≥10,000/mm³	110/177 (62.1)	93/171 (54.4)	0.78	0.08
Cytogenetic profile				
Favorable	15/38 (39.5)	14/51 (27.5)	0.61	0.19
Indeterminate	57/89 (64.0)	51/85 (60.0)	0.80	0.24
Intermediate	80/142 (56.3)	57/127 (44.9)	0.67	0.02
Unfavorable	46/59 (78.0)	45/63 (74.1)	0.85	0.45



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Median Overall Survival According to Cytogenetic Risk and Mutation Status

	Standard Dose ($45\ mg/m^2/d$)	High Dose ($90\ mg/m^2/d$)	*P*-value
All patients (n=330, 327)	15.7 mo	23.7 mo	0.003
Cytogenetic Profile			
Favorable, Intermediate (n=180, 178)	20.7 mo	34.3 mo	0.004
Unfavorable (n=59, 63)	10.2 mo	10.4 mo	0.45
Mutation Status			
FLT3-ITD-positive (n=83, 64)	10.2 mo	15.2 mo	0.09
FLT3-ITD-negative (n=215, 241)	18.9 mo	28.6 mo	0.01
MLL-PTD-positive (n=16, 15)	16.2 mo	19.0 mo	0.30
MLL-PTD-negative (n=290, 296)	15.1 mo	25.0 mo	0.002

ITD = internal tandem duplication; PTD = partial tandem duplication

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Adverse Events During Induction Therapy

Adverse Event (Grade 3/4)	Standard Dose ($45\ mg/m^2/d$) (n = 318)	High Dose ($90\ mg/m^2/d$) (n = 315)
Low hemoglobin	77%	77%
Low blood count Leukocytes Neutrophils Platelets	 97% 97% 97%	 98% 93% 98%
Transfusion required Platelets Packed red cells	 60% 60%	 64% 59%
Hemorrhage with Gr3/4 low platelet count	9%	11%
Febrile neutropenia	35%	36%
Infection with Gr 3/4 neutropenia*	47%	49%
Cardiac event (Gr 3-5)	7%	8%

*Grade 5 Infection with Gr 3/4 neutropenia: Standard dose (n = 1), High dose (n = 8)

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Summary and Conclusions

- Induction therapy with high-dose daunorubicin (90 mg/m^2/d) significantly improved overall survival and complete remission rate (CR) compared to standard-dose daunorubicin, particularly in younger patients (<50 years) with favorable- or intermediate-risk cytogenetics.
  - OS (All patients): 23.7 mos vs 15.7 mos, p=0.003
  - OS (Favorable/Intermediate risk): 34.3 mos vs 20.7 mos, p=0.004
  - CR: 70.6% vs 57.3%, p < 0.001
- Higher-dose daunorubicin did not significantly increase the frequency of adverse events or affect the delivery of consolidation therapy.
  - Received consolidation therapy: 57.8% vs 49.4%, p=0.03
- In younger patients, a dose of daunorubicin exceeding the standard 45-mg/m^2 dose for induction should be considered a new standard of care.

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