5 Minute JournalClub

Anthracycline Dose Intensification in Acute Myeloid Leukemia (AML)

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CME INFORMATION

OVERVIEW OF ACTIVITY

Acute myeloid leukemia (AML) and the myelodysplastic syndromes (MDS) account for approximately 20 percent of all hematologic cancer and related hemopathies diagnosed on an annual basis. Emerging and continuing clinical research has resulted in an increased understanding of the heterogeneous nature of these diseases and in the availability of novel treatment strategies and options. In order to offer optimal patient care — including the option of clinical trial participation — the practicing medical oncologist must be well informed of the rapidly evolving data sets in AML and MDS. To bridge the gap between research and patient care, this CME activity will deliver a serial review of recent key presentations and publications and expert perspectives on how these new evidence-based concepts can be applied to routine clinical care. This activity will assist medical oncologists and other cancer clinicians in the formulation of optimal clinical management strategies for AML and MDS.

LEARNING OBJECTIVE

- Identify younger patients with newly diagnosed AML who should receive higher doses of daunorubicin-based induction therapy.

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FACULTY — The following faculty (and their spouses/partners) reported real or apparent conflicts of interest, which have been resolved through a conflict of interest resolution process:

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Consulting Agreement and Stock Ownership: Celgene Corporation; Paid Research: Celgene Corporation, Johnson & Johnson Pharmaceuticals.

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Oncologists who partake in our **audio series** while they drive in their cars, run on their treadmills or work in their gardens seem to enjoy the often prolonged and Talmudic discussions with master clinical investigators who dissect every corner of medical oncology, but those of you out here in Web World are far more constrained by time, and to that end we offer another iteration of our 5-Minute Journal Club. This latest installment consists of a series of four emails sent at weekly intervals that will highlight approximately 20 recently published journal articles and meeting presentations on MDS/AML deemed by our faculty of Drs Steve Gore and Gail Roboz to be of great relevance to busy physicians in practice. The emails will introduce a specific set of papers and provide links to quickly access slides and faculty comments further explaining the findings from each report.

My favorite out of this first set is the ***JCO* paper by Gardner and colleagues** of a recent trial of 153 patients with newly diagnosed AML receiving induction treatment in a protected environment who were randomly assigned to a cooked (neutropenic) versus an uncooked diet. This fascinating study reveals that the prior belief, upheld by many, that uncooked foods would increase the rates of major infections or death in these patients was unfounded, and while this paper does not bring us any closer to a cure for this dreadful disease, it does provide some solace that those enduring the terrifying experience of induction therapy can enjoy a crispy apple or some grapes while they await the next step in their difficult journey.

Clearly the most practice- and paradigm-changing study profiled herein is the ***Lancet Oncology* paper by Fenaux and colleagues** demonstrating the most important advance in MDS in a long time, specifically that the use of the hypomethylating agent 5-azacitidine was associated with an impressive improvement in overall survival from 15 to 24.5 months in patients with high-risk disease. At a recent CME meeting we hosted in Naples, Florida, Dr Hagop Kantarjian commented that he believes the key to the efficacy of this intriguing agent is the ability to deliver multiple treatment cycles, which was more important than achieving a complete clinical response. He suggested that unlike ARA-C in AML, 5-azacitidine should be continued in MDS even if response is not observed in the first one or two treatment cycles.

Another critical MDS paper included here is a study by Dr Kantarjian examining MD Anderson's rich experience with patients with MDS and chromosome 5 abnormalities. The paper clearly demonstrates the heterogeneity within this uncommon patient subset, in which lenalidomide is often used. Interestingly, in his Naples presentation,

Dr K noted that he thinks this fascinating immunomodulatory agent is also a rational consideration in some patients with MDS *without* chromosome 5 abnormalities, specifically those with low-risk disease and transfusion dependence. In that setting, he believes, lenalidomide results in a transfusion independence rate of about 25 percent.

Finally, we have **an AML paper** that somehow escaped Dan Haller's *JCO* clutch and slipped into the *New England Journal* — a study demonstrating more CRs and better survival in patients receiving 90-mg/m^2 of daunorubicin than those receiving 45-mg/m^2. Dr Roboz questions the relevance of these findings because of the 45-mg/m^2 control arm, as she believes most physicians are using the 60-mg/m^2 dose.

Stay tuned for our next journal club, in which we review yet another paper by the prolific Dr Kantarjian proposing a new prognostic model for MDS, an MDS study evaluating the impact of pretransplant 5-azacitidine on the risk of post-transplant relapse, a study of decitabine in older patients with MDS and another paper on 5-azacitidine in MDS evaluating three different doses/schedules.

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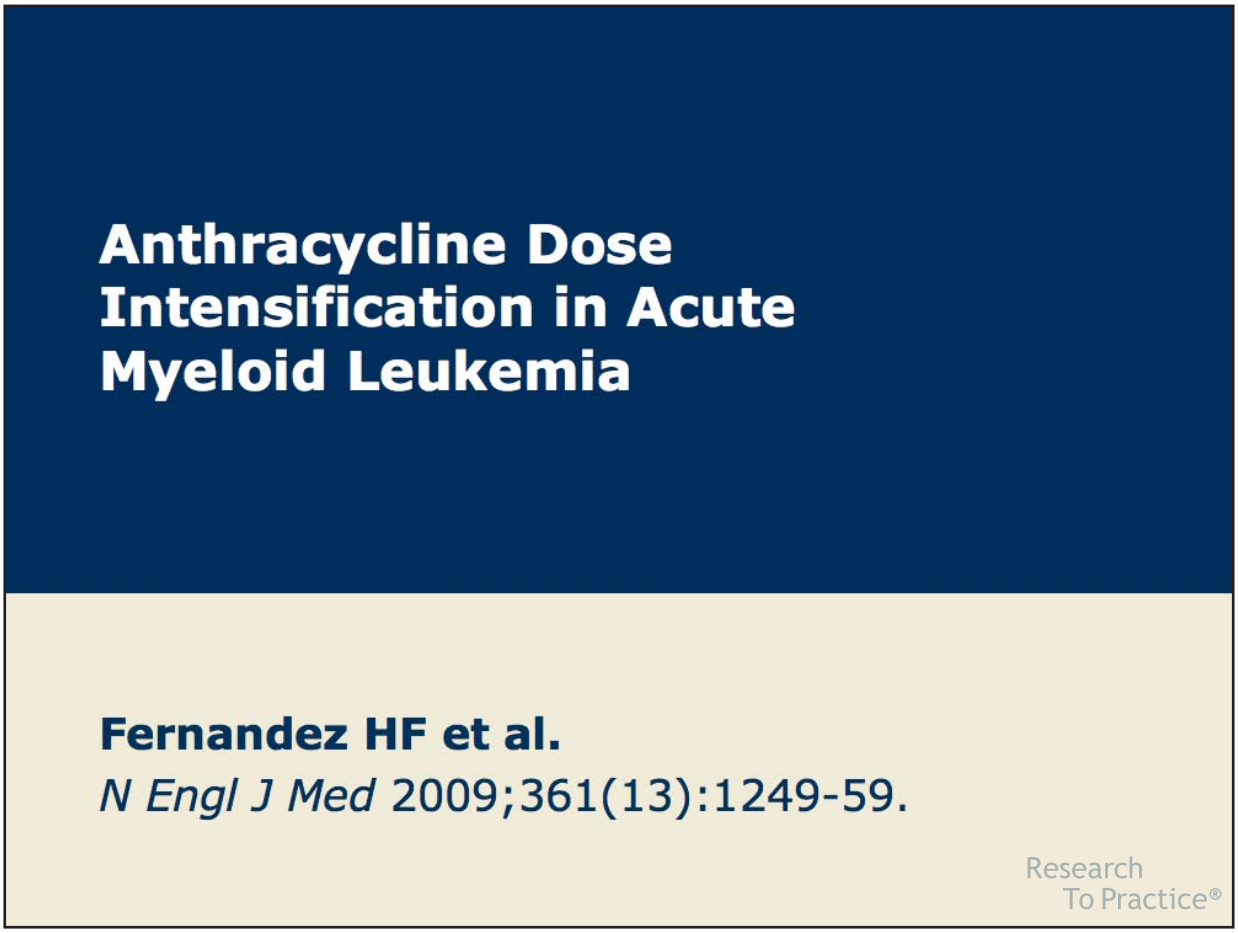
Anthracycline Dose Intensification in Acute Myeloid Leukemia (AML)

Presentation discussed in this issue:

Fernandez HF et al. **Anthracycline dose intensification in acute myeloid leukemia.** *N Engl J Med* 2009;361(13):1249-59. **Abstract**

Slides from the journal article and transcribed comments from recent interviews with Gail J Roboz, MD (10/6/09) and Steven D Gore, MD (10/8/09) below



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.

Fernandez HF et al. *N Engl J Med* 2009;361(13):1249-59. © 2009

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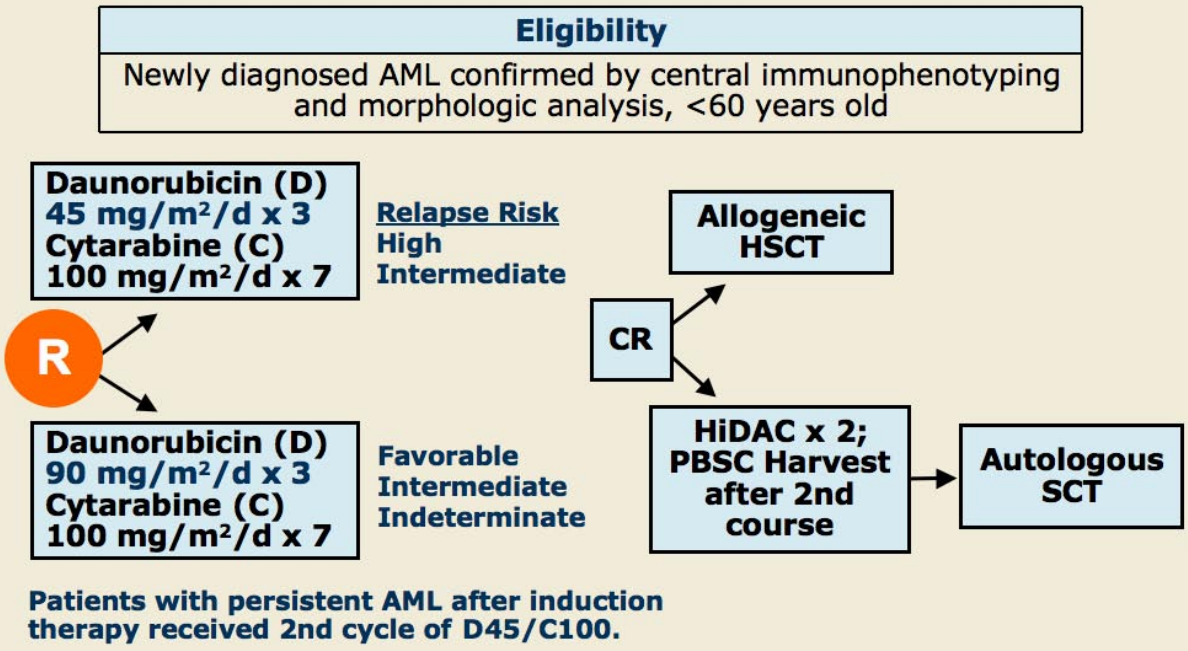
ECOG-E1900: Phase III, Randomized Study (N = 657)



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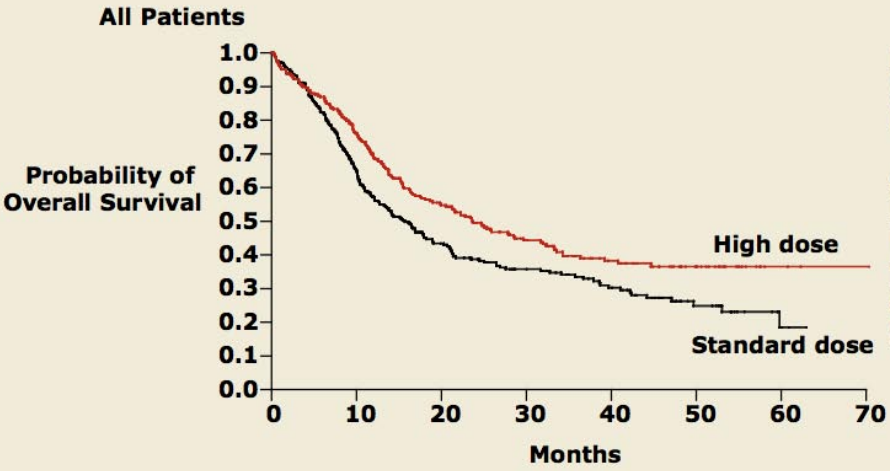
Overall Survival (Intent-to-Treat): All Patients



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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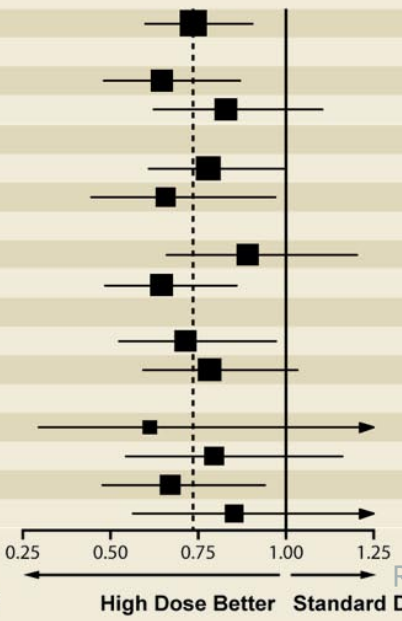
Hazard Ratios for Death According to Subgroup

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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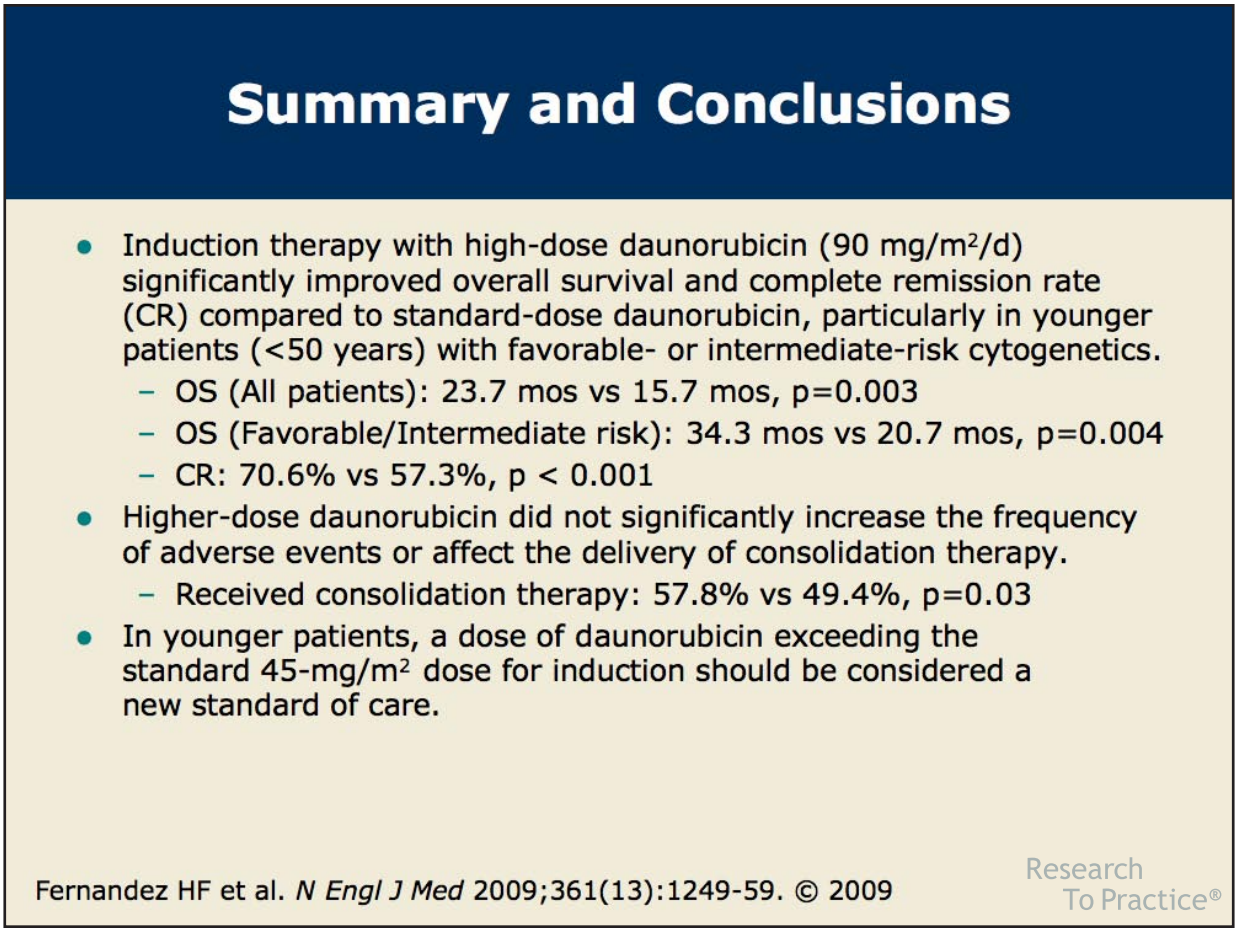

GAIL J ROBOZ, MD: This was a beautifully done study, which clearly shows that the higher daily dose of anthracycline at 90 mg/m^2 is better than the 45 mg/m^2 dose. The only problem with the study is that it uses a control arm of 45 mg/m^2, which is a lower dose than a lot of people use for AML. It has been standard for several years to use 60 mg/m^2 as the induction dose of daunorubicin. Many physicians question whether daunorubicin 90 mg/m^2 is better than 60 mg/m^2, and unfortunately, this study did not answer that question. Physicians who have been using 45 mg/m^2 as their standard dose should change to 90 mg/m^2. For those who have been using 60 mg/m^2 as their off-study treatment dose for induction, they do not know what to do. I would say that the experts are divided as to whether or not this represents a new standard.

STEVEN D GORE, MD: This is an important study, which demonstrates that a higher dose of anthracycline had an effect on overall survival in patients, particularly those with favorable or intermediate cytogenetics. However, it did not have an effect in patients with high-risk cytogenetics or in patients who had FLT3 mutations or MLL partial tandem duplication. I believe that this is a bit of a game changer, potentially, for patients with intermediate- or lower-risk AML who are receiving standard induction regimens. The problem, of course, is that you do not always have all of this cytogenetic and mutational analysis information before therapy is initiated. I believe the default will be that everybody should probably receive the higher dose until proven otherwise. If

you find out the patients are in one of these groups that do not benefit, you would not necessarily continue with the higher dose during consolidation.

Dr Roboz is Associate Professor of Medicine and Director of the Leukemia Program at Weill Medical College of Cornell University at NewYork-Presbyterian Hospital in New York, New York.

Dr Gore is Professor of Oncology at Johns Hopkins University in Baltimore, Maryland.