



**Phase II Study of Clofarabine
for Older Patients with
Treatment-Naïve 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

- Evaluate the Phase II study results of single-agent clofarabine for elderly patients with AML.

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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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Inside this issue: Four interesting AML nuggets:

1. **A Phase II study** evaluating clofarabine in 112 older patients (median age 71) with AML and one or more adverse prognostic factors. Treatment was “well tolerated” and resulted in 38% CRs.
2. **A Phase II study** of the hypomethylating agent decitabine in 55 older patients (median age 74) with AML. Morphologic CR was observed in 24%; febrile neutropenia was observed in 24%.
3. **A literature review** suggesting that assays for NPM1mut and FLT3 ITDneg could be the new ER and HER2 of AML. (Ok, maybe that is an overstatement, but these are highly prognostic and predictive.)
4. **A retrospective analysis** demonstrating roughly similar results with allogeneic hematopoietic stem cell transplant in patients with AML over and under age 65.

Editor’s comment: Who should treat patients with AML?

Mike Schwartz, a Memorial-trained medical oncologist practicing in Miami Beach, is one of several dozen “master clinicians” across the country who have assisted us with our CME programs. Mike’s most recent contribution was helping us plan an upcoming **Satellite Symposium** that we will host in New Orleans on Friday night, December 4, preceding the ASH annual meeting.

Dr Schwartz will join four other community-based physicians as they present challenging cases of AML, MDS, CML, and myeloma from their practices to our all-star faculty. In addition to discussing these carefully selected patients, we will also reveal the results of our recent **national Patterns of Care survey** of US-based oncologists, specifically focusing on the management of the cases being presented at the meeting.

One interesting survey question that we will discuss live is “Do you treat some or most patients with AML or do you generally refer them to a tertiary center?” To my mild surprise, more than two thirds of the survey respondents generally manage these patients themselves, and that includes Mike, who will present a 59-year-old woman recently diagnosed with AML.

Our prior surveys have documented that oncologists in practice see about as many cases of breast cancer a year as breast cancer investigators, but AML is a complicated disease that occurs at less than one tenth the frequency.

Of course there is more than science required in these intense situations, as evidenced by Mike's patient, an Asian woman, who asked if she could take traditional therapeutic herbs during chemo (Mike said "No," as did 79 percent of the oncologists surveyed).

Certainly physicians who offer patients a local means to receive treatment for a very scary disease must do their best to keep up with the gradual but definite progress in AML. In New Orleans, we'll see what our faculty has to say about Mike's patient and whether they think she, like many others, can be effectively managed in the community. From my standpoint, this woman is fortunate to be receiving care from one of the many, many extraordinary clinicians working outside of academic medicine.

Next up on 5-Minute Journal Club: The final four papers highlighted in our series along with results from our Patterns of Care study documenting oncologists' management of MDS.

Neil Love, MD
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Phase II Study of Clofarabine for Older Patients with Treatment-Naïve AML

Presentations discussed in this issue:

Erba HP et al. **Phase II study of single agent clofarabine in previously untreated older adult patients with acute myelogenous leukemia (AML) unlikely to benefit from standard induction chemotherapy.** *Blood* 2008;112:558. [**Abstract**](#)

Kantarjian M et al. **Classic II: Updated remission duration and survival results of single agent clofarabine in previously untreated older adult patients with acute myelogenous leukemia and at least one unfavorable baseline prognostic factor.** *Haematologica* 2009;94;[**Abstract 0835**](#).

Slides from a presentation at ASH 2008, transcribed comments from a recent presentation by Hagop M Kantarjian, MD (10/17/09) and recent interviews with Gail J Roboz, MD (10/6/09) and Steven D Gore, MD (10/8/09) below

A Phase II Study of Single Agent Clofarabine in Previously Untreated Older Adult Patients with Acute Myelogenous Leukemia (AML) for Whom Standard Induction Chemotherapy is Unlikely to be of Benefit: CLO24300606/CLASSIC II

Erba HP et al.

Blood 2008;112: Abstract 558

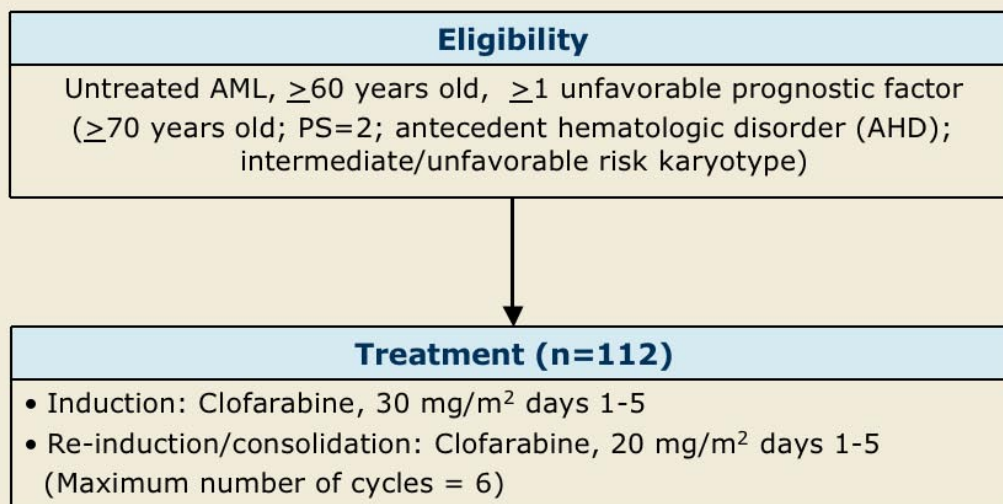
Introduction

- Older patients with AML have inferior treatment outcomes due to increased incidence of patient- and disease-related adverse risk factors:
 - High treatment-related mortality rate
 - Lower CR rates and short remission duration
 - Inadequate outcomes with cytarabine and anthracycline induction therapy for patients with unfavorable prognostic risk factors
- **Current study objectives:**
 - Primary: Determine the overall remission rate (ORR) with clofarabine in patients ≥ 60 years old with untreated AML and ≥ 1 adverse prognostic factor
 - Secondary: 30-day mortality; disease-free survival (DFS); remission duration; overall survival (OS); safety and tolerability

Source: Erba HP et al. *Blood* 2008;112: Abstract 558

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Phase II Study of Clofarabine in Older Patients with AML



Source: Erba HP et al. *Blood* 2008;112: Abstract 558

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Results: Response by Independent Review Panel (IRRP) (n=112)

Response	N	Response Rate, % (95% CI)
ORR	51	46% (36, 55)
Complete remission (CR)	42	38% (29, 47)
Complete remission with incomplete platelet recovery (CRp)	9	8% (Not reported)
Partial remission	4	4% (Not reported)
Remissions (CR + CRp) after cycle 1 (induction)	38	8% (Not reported)
Remissions (CR + CRp) after cycle 2 (re-induction)	13	25% (Not reported)

Median time to ORR = 5.1 weeks

Median time to peripheral blood blast clearance: 5 days

Median duration of response for CR/CRp = 56 weeks*

Source: Erba HP et al. *Blood* 2008;112: Abstract 558

*Updated results, Kantarjian M et al. *Haematologica* 2009;94[S2];336. Abstract 0835

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Results: Survival

Survival	
Median DFS (CR/CRp)	37 weeks
Median OS	
All patients (n=112)	41 weeks
Patients with CR/CRp	59 weeks
Patients with CR	72 weeks
30-day mortality	
All patients (n=112)	9.8%
Patients < 70 years old	4.7%
Patients ≥ 70 years old	13.0%

Source: Kantarjian M et al. *Haematologica* 2009;94[S2];336. Abstract 0835

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Drug-Related Adverse Events in $\geq 10\%$ of Patients

Adverse Event	Number of Patients		
	All Grades	Grade 3	Grade 4/5
Nausea	69	4	0
Febrile neutropenia	49	46	2
Vomiting	43	0	0
Diarrhea	38	3	0
Rash	34	2	0
Fatigue	20	3	0
Pneumonia	17	9	5
Anorexia	15	3	0
Mucosal inflammation	13	3	0

Source: Erba HP et al. *Blood* 2008;112: Abstract 558

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Conclusions

- Single-agent clofarabine is an active agent with acceptable toxicity in a well-defined population of older patients with AML who do not typically benefit from standard induction chemotherapy
 - The response rate was not affected by adverse risk factors such as age ≥ 70 years, PS 2, AHD and unfavorable blast karyotype
 - DFS and OS compare favorably to historical experience with other regimens
 - Median DFS = 37 weeks; median OS = 41 weeks; all-cause 30-day mortality = 9.8%*
 - Complete remissions appear to be durable (median DOR = 56 weeks)
- A Phase III study of clofarabine with cytarabine versus cytarabine alone is currently open for enrollment: NCT00317642, CLASSIC I

Source: Erba HP et al. *Blood* 2008;112: Abstract 558

*Updated results, Kantarjian M et al. *Haematologica* 2009;94[S2];336. Abstract 0835

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Source: Erba HP et al. *Blood* 2008;112: Abstract 558

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DR KANTARJIAN: In older patients, we are hoping for something good with clofarabine, an adenosine analog like CDA and fludarabine, but it's completely different in the sense that it doesn't work in lymphoid tumors, except for pediatric leukemias, but it has a major effect in acute myeloid leukemia (AML) and in myelodysplastic syndromes.

We developed this Phase II study three years ago and enrolled older patients with AML with adverse features, and we demonstrated that the drug is associated with a response rate of 40 percent that persists across combinations of adverse factors, with a low mortality of under 10 percent at four weeks. What we see in this study is that once the patients have a response, it is durable beyond a year, and the median survival is approximately nine months with the one-year survival rate at approximately 45 percent. The data are encouraging, and we are proceeding with randomized trials with this drug.

DR ROBOZ: This is an interesting paper for clinicians because fairly few drugs out there have a meaningful complete remission rate in AML. Physicians need to be aware of these data, because clofarabine is a single-agent drug with a relatively high complete remission rate and a favorable toxicity profile. Currently, a randomized cooperative group trial of clofarabine with cytarabine versus cytarabine alone is being conducted and physicians need to try to accrue patients to it.

DR GORE: In this study, 112 elderly patients with AML received single-agent clofarabine, resulting in an overall response rate of 46 percent, with complete responses of 38 percent. There is no question that this drug warrants further investigation.

Dr Kantarjian is Chairman and Professor of the Leukemia Department at The University of Texas MD Anderson Cancer Center in Houston, Texas.

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.