5 Minute JournalClub

SPECIAL EDITION
Issue 2, 2011

Clinical Trial Results with Novel Agents and Regimens for the Treatment of Newly Diagnosed or Relapsed/Refractory AML/MDS, Including in the Elderly

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CME INFORMATION

OVERVIEW OF ACTIVITY

Each year, thousands of clinicians and basic scientists sojourn to the American Society of Clinical Oncology (ASCO) Annual Meeting to learn about recent clinical advances that yield alterations in state-of-the-art management for all tumor types. Attracting tens of thousands of attendees from every corner of the globe to both unveil and digest the latest research, ASCO is unmatched in attendance and clinical relevance. Results presented from ongoing trials lead to the emergence of new therapeutic agents and changes in the indications for existing treatments across all cancer medicine. Despite the importance of the conference, the demands of routine practice often limit the amount of time oncology clinicians can realistically dedicate to travel and learning. To bridge the gap between research and patient care, this CME activity will deliver a review of the key presentations from the ASCO Annual Meeting 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 diverse forms of cancer.

LEARNING OBJECTIVES

- Consider emerging data on the use of cytarabine in combination with clofarabine for older patients with relapsed or refractory acute myelogenous leukemia (AML).
- Consider the inclusion of decitabine in the treatment algorithm for older patients with newly diagnosed AML.
- Describe Phase I efficacy outcomes with sequential azacitidine and lenalidomide for elderly patients with AML.
- Describe Phase I/II efficacy outcomes with the MEK1/2 inhibitor GSK1120212 in patients with relapsed/refractory myeloid cancer.

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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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No real or apparent conflicts of interest to disclose.

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This activity is supported by educational grants from Bristol-Myers Squibb Company, Celgene Corporation and Genentech BioOncology.

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To go directly to the slides and investigator commentary for the featured abstracts, **click here**.

An oncology specialist would be hard pressed to find a better hour of television than the first half of the oral leukemia/myelodysplasia plenary session from ASCO 2011. This riveting segment of the conference, available for your viewing pleasure as part of the virtual meeting, began with 2 complementary presentations of Phase III trials evaluating the JAK1/2 inhibitor ruxolitinib **(ab 6500**, **ab LBA6501)** in patients with myelofibrosis. These were followed by a fascinating BCR-ABL mutation analysis from the ENESTnd CML study **(ab 6502)** comparing nilotinib to imatinib and then a brilliant follow-up discussion by Dr Ross Levine outlining a new paradigm in myeloproliferative disorders focused on the search for mutations and related novel blocking agents. These 3 presentations and 14 other compelling ASCO heme-onc data sets are detailed in our slide sets and profiled below in this, the second half of our super-succinct special edition *5-Minute Journal Club*.

1. Ruxolitinib in myelofibrosis

As mentioned above, this trial duet occupies a unique spot on the ASCO highlights reel, and while our understanding of the exact mechanism of action of this oral TKI may be somewhat hazy and may relate to reduction in elevated cytokine levels, what is crystal clear is that this uncommon but merciless disease has instantly entered a new era. The US-based COMFORT-I study evaluating ruxolitinib versus placebo had a number of interesting and innovative features, including the use of MRI to objectively evaluate spleen size and electronic daily diaries to record patient symptoms. The dramatic waterfall plots visibly illustrate how treatment at least temporarily reversed an otherwise downhill course in most patients.

2. CML

Dr Giuseppe Saglio presented the other previously discussed ASCO standout — the landmark substudy from the ENESTnd trial **(ab 6502)** demonstrating that prior to treatment patients had almost no BCR-ABL mutations but after therapy a fascinating panoply of alterations was observed in some individuals. Dr Levine predicted that in the near future, mutation assays will be regularly integrated into the treatment algorithm.

Additionally, 24-month follow-up from 2 key Phase III studies (ENESTnd **[ab 6511]** and DASISION **[ab 6510]**) was also unveiled in Chicago, suggesting greater efficacy and perhaps less toxicity with up-front treatment with the second-generation TKIs nilotinib and dasatinib when compared to imatinib.

3. Inotuzumab ozogamicin (our vote for name of the year)
This antibody-drug conjugate in the lineage of brentuximab vedotin in lymphoma and T-DM1 in HER2-positive breast cancer links an anti-CD22 antibody to a cytotoxic agent from the calicheamicins class (runner up). The ASCO findings **(ab 6507)** in relapsed/refractory ALL demonstrated some type of CR in 61% of patients.

4. Myeloma
For more than a year we have witnessed the evolution of data from 2 major trials (CALGB, French IFM group) demonstrating an impressive delay in disease progression but the suggestion of an increased risk of second primary cancers (SPC) with 2 years of lenalidomide maintenance following stem cell transplant (SCT). At ASCO, 3 additional reports **(ab 8007, ab 8008, ab 8009)** have for the moment reinforced the concept that if there is an SPC signal it is relatively modest in magnitude and far outweighed by the antimyeloma benefit of maintenance len.

The other much-discussed myeloma paper was a landmark Italian study **(ab 8020)** that for the first time evaluated the role of autologous SCT in the era of novel antimyeloma agents. A progression-free survival benefit was reported with SCT, but other maturing studies are evaluating this important question.

5. CLL
Maybe the most exciting development in B-cell neoplasm research is the rapid evolution of small molecules that block B-cell receptor signaling, and at ASCO we saw more to be optimistic about with a report on the Bruton's tyrosine kinase inhibitor PCI-32765 in CLL. In this Phase Ib/II single-agent study **(ab 6508)**, response rates in excess of 50% were observed with minimal toxicity.

6. Diffuse large B-cell lymphoma
The lack of progress in this common cancer since the introduction of rituximab was highlighted again this year with 1 trial failing to show an advantage with dose-dense R-CHOP **(ab 8000)** and another showing no important survival benefit to consolidation autotransplant after R-CHOP induction **(ab 8001)**.

7. AML
AML in the elderly — a true clinical conundrum — was the subject of 3 underwhelming ASCO reports. The first **(ab 6503)** showed a modest benefit that was counterbalanced by a relatively high early mortality rate when clofarabine was combined with Ara-C. The

second **(ab 6504)** demonstrated a modest benefit for decitabine, but discussant Dr Gail Roboz verbalized hope that better outcomes might be observed in her ongoing trial evaluating 10 days of decitabine combined with the proteasome inhibitor bortezomib. The third study **(ab 6505)** was a Phase I effort evaluating a sequential regimen of azacitidine and lenalidomide that resulted in CRs in 7 of 16 patients.

Finally, we saw another interesting AML study perhaps suggesting a new model for the real-time personalized treatment of the disease. In this Phase I/II trial **(ab 6506)**, the MEK1/2 inhibitor GSK1120212 was shown to have specific activity in patients with RAS mutations.

Coming soon, an online quintet of virtual presentations delving into new developments in non-small cell lung cancer.

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Miami, Florida

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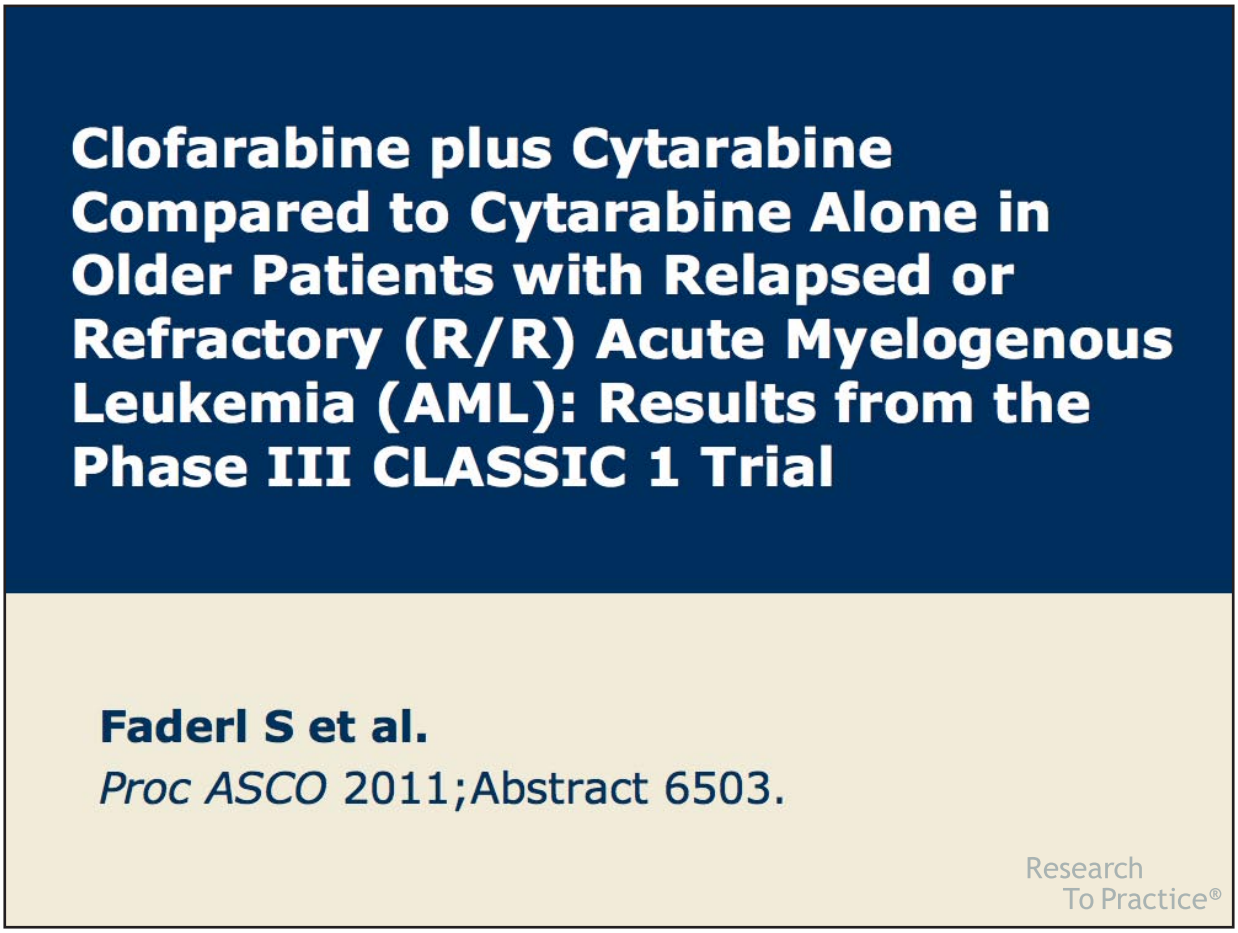
Clinical Trial Results with Novel Agents and Regimens for the Treatment of Newly Diagnosed or Relapsed/Refractory AML/MDS, Including in the Elderly

Presentation discussed in this issue

Faderl S et al. **Clofarabine plus cytarabine compared to cytarabine alone in older patients with relapsed or refractory (R/R) acute myelogenous leukemia (AML): Results from the phase III CLASSIC 1 trial.** *Proc ASCO* 2011;**Abstract 6503**.

Slides from a presentation at ASCO 2011 and comments from Susan M O'Brien, MD



CLASSIC 1 Study Design

Eligibility (N = 320)

- **Age ≥ 55 years**
- **R/R AML**
- **At least 1 but no more than 2 prior treatments**
- **ECOG PS 0-2**

R

n = 162 → **Clofarabine 40 mg/m² IV daily x 5 plus Ara-C 1 g/m² IV daily x 5**

n = 158 → **Placebo IV daily x 5 plus Ara-C 1 g/m² IV daily x 5**

Stratification:
- Refractory (REF): No response or first complete remission (CR1) < 6 months
- Relapsed (REL): CR1 ≥ 6 months

Primary objective:
- Overall survival

Secondary objectives:
- CR rate, overall response rate (ORR), event-free survival (EFS), disease-free survival (DFS), duration of remission (DOR), safety

Faderl S et al. *Proc ASCO* 2011;Abstract 6503.

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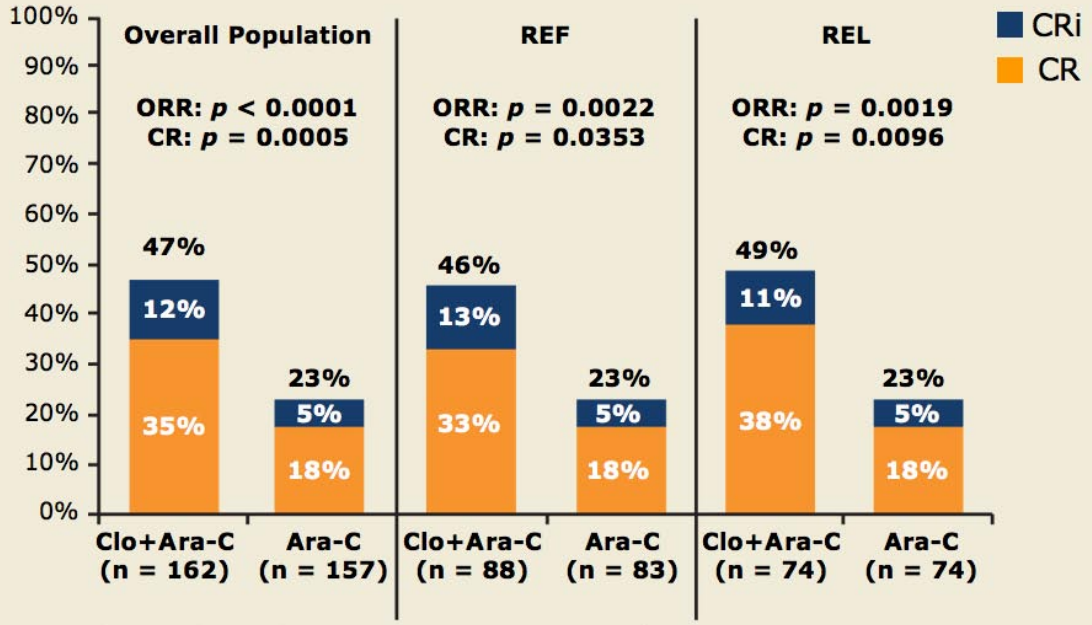
Overall Response Rate*



* By independent response review panel

Faderl S et al. *Proc ASCO* 2011;Abstract 6503.

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Event-Free Survival

	Hazard ratio (Clofarabine + Ara-C vs Ara-C alone)	*p*-value
Overall population	0.63	0.0001
Relapsed patients	0.57	0.0022
Refractory patients	0.67	0.0131

Faderl S et al. *Proc ASCO* 2011;Abstract 6503.

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Overall Survival

	Clofarabine + Ara-C (n = 162)	Ara-C (n = 158)	Hazard ratio	*p*-value
Median OS	6.6 months	6.4 months	1.00	0.9951
Relapsed patients	NR	NR	0.85	0.3963
Refractory patients	NR	NR	1.13	0.4674

NR, not reported

Faderl S et al. *Proc ASCO* 2011;Abstract 6503.

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Safety

	Clofarabine + Ara-C (n = 161)	Ara-C (n = 155)
Any Grade ≥3 adverse event (AE)	98%	86%
Discontinuation of drug due to AE	11%	3%
Serious AE	60%	49%
Death due to AE	14%	5%
Death due to treatment-related AE	6%	2%
30-day mortality	16%	5%
60-day mortality	24%	17%

Faderl S et al. *Proc ASCO* 2011;Abstract 6503.

Safety (continued)

	Clofarabine + Ara-C	Ara-C
Serious AEs (≥5% in either arm)		
Infection	38%	22%
Pneumonia	8%	8%
Sepsis	5%	2%
Febrile neutropenia	16%	12%
Pyrexia	4%	6%
≥Grade 3 AE (noninfectious; ≥10% in either arm)		
Febrile neutropenia	47%	34%
Hypokalemia	18%	10%
Thrombocytopenia	16%	17%
Anemia	13%	8%
Neutropenia	11%	9%
Increased ALT/AST	21%	5%

Faderl S et al. *Proc ASCO* 2011;Abstract 6503.

Author Conclusions

- Overall survival did not differ between treatment arms.
- Statistically significant improvement in secondary endpoints was reported.
  - Overall response rates and complete response rates doubled
  - Significantly prolonged event-free survival
- Higher early mortality rate was reported in the clofarabine and cytarabine arm.
- Long-term study follow-up continues.
- Clofarabine in the treatment of adult patients with AML continues to be investigated in randomized cooperative group studies.

Faderl S et al. *Proc ASCO* 2011;Abstract 6503.

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Investigator Commentary: The CLASSIC 1 Study of Cytarabine with or without Clofarabine for Older Patients with Relapsed/Refractory AML

This study evaluated clofarabine at 40 mg/m^2 daily times 5 and high-dose cytarabine versus high-dose cytarabine alone in older patients with relapsed/refractory AML. The authors reported the CR rate to be almost doubled with clofarabine and Ara-C. The event-free survival was also much improved, but the overall survival was no different. The primary reason for that was that the induction mortality was higher. This is a theme also reported in other trials evaluating Ara-C in combination with a second agent.

One point is that the clofarabine dose was probably too high. It would be interesting to have data evaluating clofarabine at a lower dose, particularly in an older patient population. It's also not clear to me why they chose to focus on older patients, because you could make the argument that if this trial hadn't been so restricted maybe the early mortality rate wouldn't have been significantly increased. I believe a 67-year-old's ability to tolerate high-dose Ara-C, even high-dose Ara-C alone, is not the same as that of a 40-year-old. I'm sure there was a rationale for the older patient population here. But in terms of the randomized trial design, the high dose of clofarabine and restricting the trial to older patients probably "put them behind the eight ball".

Susan M O'Brien, MD